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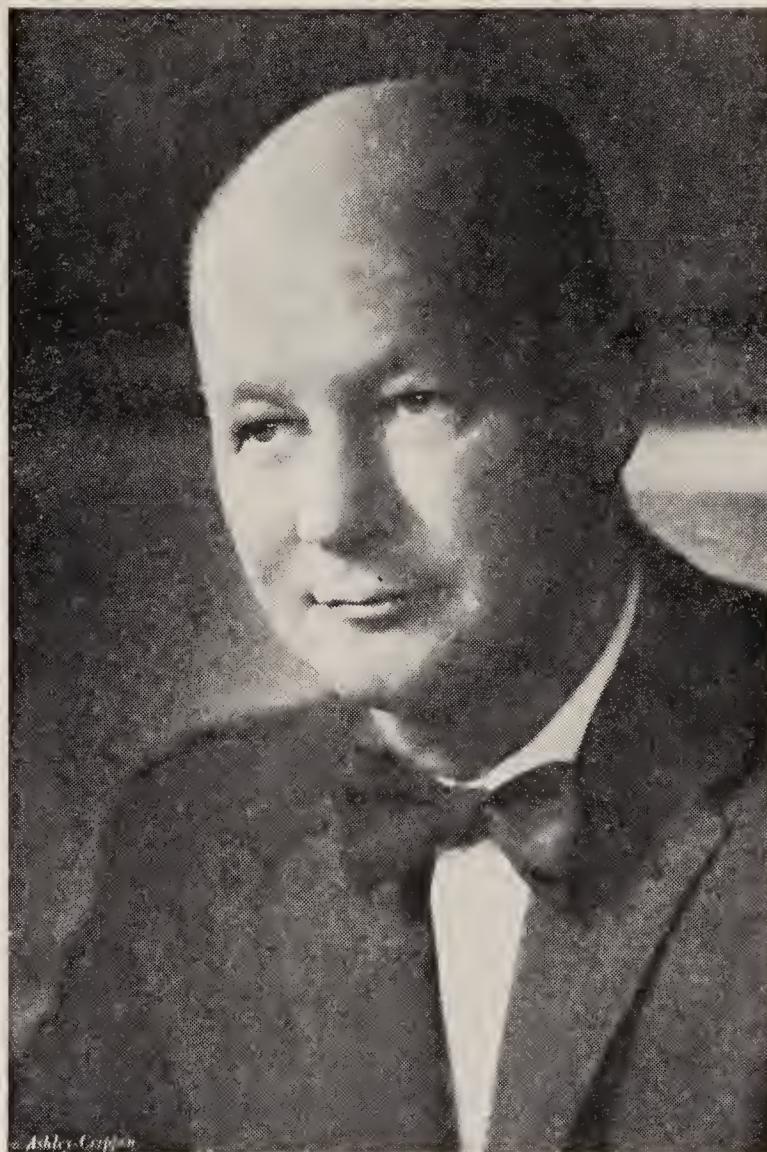
Guest Editorial

WILLIAM THORNTON MUSTARD

M.B.E., M.D., M.S. (TOR.),
F.R.C.S.(C), F.A.C.S., F.A.C.C.

Born on August 8, 1914, in Clinton, Ontario, William Mustard attended the University of Toronto (1931-1937). His internship at the Toronto General Hospital set the field for an extremely diversified post-graduate career. He was decorated while commanding a field surgical unit in World War II (M.B.E.). A fellow in both the Royal College and American College of Surgeons, he recently received a further fellowship in the American College of Cardiology. Dr. Mustard actually started his career as an orthopedic surgeon and gradually had two specialist's fields—orthopedic and cardiac surgery. In 1964 he found it necessary to make a choice—cardiac surgery. Dr. Mustard is presently Chief of Cardiovascular Surgery at the Hospital for Sick Children, Toronto, and Associate Professor of Surgery at the University of Toronto. He is author of over 100 scientific publications. One of his outstanding contributions has been the development of a procedure for the correction of transposition of the great vessels. It was first performed in 1963 and is now used all over the world.

Dr. Mustard is married and has 2 sons and 5 daughters. His hobby is his summer home on Lake Kawagama.



It has been my good fortune to witness and take part in the greatest surgical explosion in history, the development of cardiac surgery. Over the past three decades we have come all the way from the ligation of the patent ductus arteriosus to the present era of heart transplantation. The reader will forgive me if I place emphasis on congenital heart disease, but this is an area in which one can write with some authority. In my undergraduate years I do not recall one single lecture on congenital heart disease.

It is now thirty years since a young surgeon, aged 34, successfully ligated a patent ductus in a five year old child. This was Dr. Robert Gross of Boston. The next step forward was the resection of coarctation of the aorta by both Gross and Craaford in 1944, and the thrilling achievement of Blalock and Taussig in 1945 of the palliative procedure for blue babies. Then in the fifties we moved into that exciting era of hypothermia, pioneered by Bigelow of Toronto, and of the extracorporeal circulation, pioneered by Gibbon of Philadelphia and brought to completion by Lillehei of Minneapolis in 1955. From that time on, scarcely over a decade ago, one had to "be a swinger and get with it" to keep abreast of the tremendous advances, not only in the treatment of congenital heart disease but of acquired heart disease as well. It is fair to say that the successful management of heart defects by the surgeon was a great stimulus to both cardiologists and pathologists. It is astonishing to realize that only during the past few years has the natural history of certain congenital cardiac defects been recognized. It had been our custom to look to the pathologists for the answer to natural history of disease but it is only recently that this discipline has been helpful to the surgeon. Accuracy of diagnosis has been greatly enhanced with the use of such diagnostic tools as cardiac catheterization and cineangiocardiology. It has become obvious that the cardiac surgeon and the cardiologist have become more closely akin than the surgeon to his contemporary surgeons. This togetherness in one system, as it were, is a healthy one and one which is being fostered in medical education. In our particular environment tribute should be paid to Dr. John Keith, pioneer of congenital heart disease, not only in this country but recognized throughout the world and the senior author of a textbook which is recognized as the best in the world.

One of the problems that the cardiac surgeon faces in the cinderella story of this field is the public appeal of heart surgery. Part of this, no doubt, comes from the numerous ballads and popular songs referring to the heart as a seat of emotion. Certainly any lay person watching a cardiac surgeon lay open the heart to repair a defect would not be too impressed with such popular songs as "My Heart Belongs to Daddy". With the possibility of heart transplants, already a technical fait accompli, the whole definition of death has to

be revised. We have been able, in the past, with the use of extracorporeal circulation and profound hypothermia, to arrest the entire circulation for periods up to half an hour, in which the patient must be pronounced dead. We are then able to reverse this process entirely by the use of extracorporeal circulation and raising the temperature and have a perfectly normal person restored, as it were, to life. Countless important physiological observations have been made such as the use of Ringer's lactate instead of blood to prime the pump and carrying your patient with no blood pressure for periods of an hour or two.

What of the future of cardiac surgery? One can only guess at the answer to this question. Certainly we rely upon the immunologist to provide us with the tools whereby we may not only be able to use homotransplants successfully with hope of long term survival, particularly in childhood, but that of heterografts as well. As far as the author is concerned the anticipation of seeing an infant, with such a complex heart defect that even palliation is impossible, growing up and developing normally with a puppy's heart to sleep with is a thrilling thought for the future.

W. T. Mustard, M.D.

Editorial

Pulling The Plug

Relatively commonly on the medical or surgical services of a large hospital, the decision to discontinue the feeder lines of a subtentorial existence must be made. Such a situation has always been fraught with moralistic argument and an ill-defined feeling of guilt on the part of the individual whose choice it is.

Western civilization places too high a value on the continuation of physical life. Very often the essence of man is forgotten in an attempt to maintain the existence of a skill which will never again function. To do so is a hollow mockery of life and an insult to the dignity and respect that death deserves.

Relatives last see their decerebrate kin as an unseeing, unfeeling, unknowing lump buried in white sheets and kept warm by tubes in and tubes out. All that is achieved is a prolongation of suffering and an unnecessary burden on society.

We are not advocating teaching medical students to kill. Rather we are saying that once the well-trained practitioner has decided, after all appropriate tests and therapy, that a decerebrate patient will remain so throughout his physical life span, then that practitioner should think seriously of not interfering with the course of nature. In the final analysis the decision and responsibility reverts, as always, to the physician-in-charge.

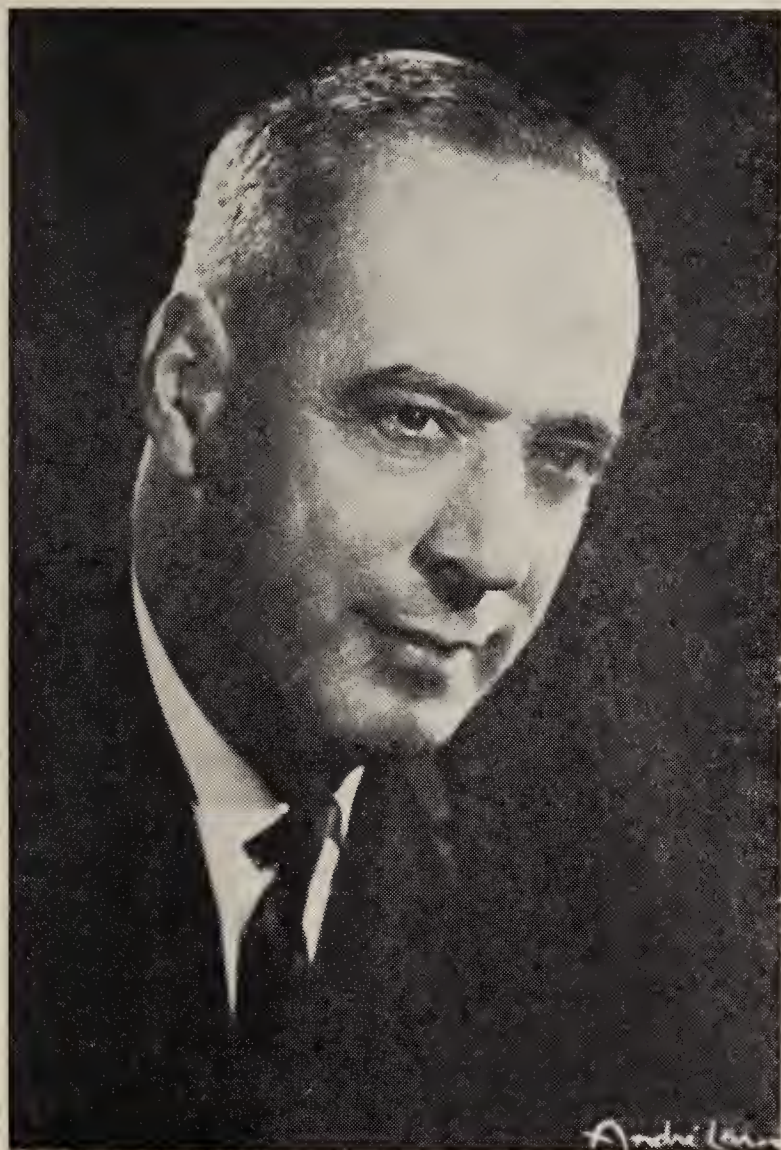
It is the opinion of the undersigned that pathognomonic signs of irreversible decerebration of whatever etiology be recognized when present, and further action be based on not only the physician's moral feelings but also his rational assessment of the situation. It is this latter facet that we too often forget in our fear of playing God.

R.M.L. J.T.M.

Heart Transplantation, A New Form Of Treatment For Irreversible Cardiac Disease

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PIERRE GRONDIN, B.A., M.D., F.R.C.S.(C)

Dr. Pierre Grondin was born in August, 1925 in Quebec city. He obtained his B.A. and M.D. degrees, Magna Cum Laude, from Laval University by 1951. Following three years of general practice in Trois-Rivières, he studied general surgery at Queen of Angels Hospital, UCLA, where he was chief resident in surgery in 1959. He received his F.R.C.S.(C) in 1959, and his F.A.C.S. in 1960. For the next year he was associate professor of clinical surgery in Laval University. He then embarked on a study of thoracic and cardiovascular surgery under Dr. Michael DeBakey in Houston, 1961, and Dr. Denton A. Cooley, Jan. 1962 to Jan. 1963. Since that time Dr. Grondin has been a leading practitioner of cardiac, thoracic and vascular surgery in Montréal. He is currently chief of the department of surgery at the Montreal Heart Institute, and among many other honours is founder of the Society of Thoracic Surgeons, and member of the Canadian Society of Cardiology and the Cardiological Society of Montréal. Dr. Grondin was the first surgeon to perform heterologous cardiac transplantation in Canada and to date has completed eight other such operations.

Since the advent of human transplantation, modern medicine is living a new and dramatic development. The intense effort of surgeons and medical laboratories throughout the world in recent years has made transplantation of essential organs a reality.

The first cardiac transplantation took place in 1964 when Dr. James Hardy and his associates transplanted the heart of a chimpanzee into a 68 year-old man. Three years later, a surgical team headed by Dr. Christiaan Barnard performed the first successful transplantation of a human heart.

Since December 1967, the procedure has been repeated with early but encouraging results. It brought a long-cherished hope to patients with incurably diseased and failing hearts. But, at the same time, new problems are born. Solutions are required to make cardiac transplantation a practical method of treatment. Among the most

immediate are: definition of the recipient, availability of a donor, technical surgical difficulties and the most important, management of the rejection phenomenon.

THE RECIPIENT

The proposed patient must have a known cardiac disease and be functional class 4 according to the classification of the New York Heart Association. Moreover transplantation should offer his only possible chance of survival. Therefore a suitable candidate is the patient with such a severe cardiac disease that no other curative or palliative treatment is known and in whom death seems imminent by all current medical evidence. He and his family must fully understand the risks and the nature of the proposed operation and the modalities of the post-operative treatment. The recipient must also have a stable personality capable of dealing with the circumstances of a special long-term management.

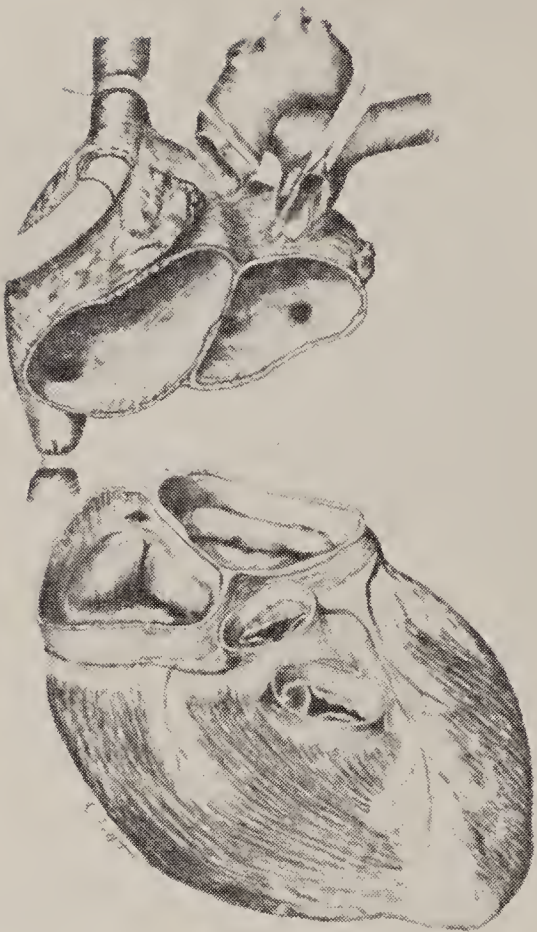


FIG. 1. Resection of the recipient's heart. Both atria and their afferent veins, the aorta and the pulmonary artery are left in place.

THE DONOR

Availability at the proper time of a suitable heart which may be removed from a dying human remains a major medical, moral and legal problem. The ideal donor is considered to be a young victim of fatal injuries not affecting the cardiovascular system. Crossmatch of his leukocytes and his ABO red blood cell group must show satisfactory compatibility with the recipient.

It must be ascertained that nothing can be done to save his life. The donor must have irreparable cerebral damage and death must be imminent based on electroencephalographic and clinical evidences of cessation of vital functions. This definition of death is difficult but crucial because no delay should be permitted between death of the donor and transplantation of his heart into the recipient.

To assure optimal protection to the myocardium, cardiac activity and circulation are maintained by mechanical pulmonary ventilation, vasopressors and other means. When cessation of cardiac action seems imminent, hypothermia and extra-corporeal circulation are instituted.

TECHNICAL ASPECTS (Fig. 1 - 2)

The heart of the donor is removed with the entire right and left atria and long segments of aorta and main pulmonary artery. Its left atrium is opened posteriorly through an incision joining all four pulmonary veins. The superior vena cava is ligated half a centimeter above its

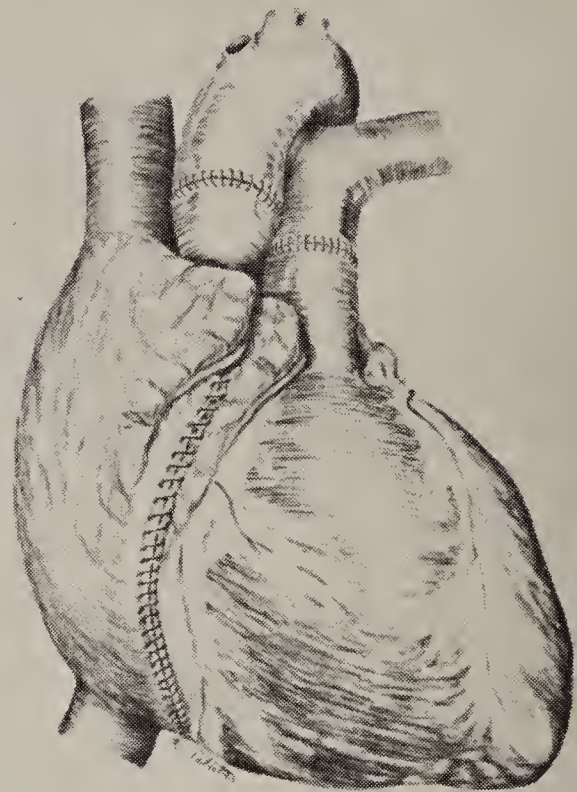


FIG. 2. Completed implantation of the donor's heart.

origin and the right atrium is opened from the anterior aspect of the inferior vena cava into the base of the auricular appendage. This incision is not made toward the superior vena cava in order to avoid injury to the nervous pathways going from the sino-auricular node to the node of Tawara. (A-V node). The donor's heart may then be cooled and its coronary arteries perfused. Cooley and Ross do not judge these means of myocardial protection necessary.

Simultaneously, the recipient is placed under cardiopulmonary by-pass by another surgical team. Venous return is achieved through cannulation of the superior vena cava and the right common femoral vein. Arterial infusion of oxygenated blood is via the right common femoral artery, or the ascending aorta. The heart is excised by dividing the aorta, the main pulmonary artery and both atria above the atrio-ventricular junction leaving most of the atrial walls. Both atrial appendages however should be removed to eliminate possible sites of thrombus formation.

Implantation of the donor's heart is started by suturing together the left atria, the right atria, the pulmonary arteries and the aortas. It is advantageous to ligate also the auricular appendages of the donor's heart to prevent embolization. Cardiac activity may resume spontaneously or with the help of an electrical shock. After closure of the

thorax, the patient is moved to an isolated room where strict sterile precautions are maintained for a two to four week period.

IMMUNO SUPPRESSIVE THERAPY

After the immediate post-operative period, immunological activity remains the major threat to the transplanted organ. Preventive therapy established for that purpose must not be too aggressive to the point of destroying all defense mechanisms of the body. Such an error usually ends up in the development of fatal infections.

Our program of immune suppression has been modeled after Starzl and others in renal and hepatic transplantations. Azathioprine (Imuran) is administered in a single dose of 3 mg/kg before the surgical procedure: it is thereafter given daily (2-3 mg/kg) in a unique dose and accordingly to the immune response of the patient. Steroids are equally important. Hydrocortisone 1 gm is injected intra-muscularly a few hours before the operation. Prednisone 200 mg is given daily in divided doses the first post-operative days and is gradually decreased to a maintenance dose of 25 to 35 mg daily.

The extensive experience of Starzl with liver transplantation has demonstrated the potent protective effect of the antilymphocyte globulin. It has permitted reduction in the amounts of Imuran and Steroids administered, thus decreasing complications associated with these drugs. Antilymphocyte serum (ALS) is administered daily for

two weeks, every other day for two weeks, twice weekly for two months and weekly thereafter.

Thymectomy performed at the time of the operative procedure may offer additional protection. The parameters of rejection repeatedly tested by Shumway and Starzl are closely followed. Always, the immune response must be kept low without submitting the patient to the risk of severe infections.

CONCLUSION

Cardiac and liver transplantations are a significant phase in the history of modern surgery. Starzl has shown that an immensely complexed organ like the liver can be successfully transplanted and can function for periods now exceeding fourteen months. Recent surgical trials have confirmed that the transplanted heart can maintain a normal pumping action for now more than nine months (Blaiberg). Is antilymphocyte globulin responsible for what seems a better control of the rejection phenomenon? Time only will answer. Continued energetic investigation is required to elucidate this immunologic resistance which remains the major problem in transplantation. How fantastic a surgical achievement it may be, human cardiac transplantation remains a clinical trial. The likelihood of such an operation to become an accepted form of treatment for incurable heart diseases is very high. More research however should continue toward artificial pumps to replace the human heart. At present, these mechanical devices because of their formidable technical problems are weak competitors to cardiac homotransplantations.

Atherosclerosis: An Etiologic And Therapeutic Review

R. M. Lifeso 6T9
J. T. Miles 6T9

In the middle of the 18th Century, William Heberden described “. . . a painful and most disagreeable sensation in the breast which seems as if it would extinguish life if it were to increase or to continue . . .”¹ Such is in fact the nature of angina pectoris, a common manifestation of ischaemic heart disease and one of the most disabling sensations known to man. Recently, a tremendous amount of time and effort has been directed towards the investigation of atherosclerotic heart disease, (ASHD), a modern epidemic. An attempt is made here to correlate some of these findings with a rational approach to the preventive as well as the therapeutic aspects of ASHD.

THE NATURE AND ETIOLOGY OF ASHD

To compare this aspect of current medical and pathological thought to a hornets' nest would be hackneyed

but appropriate. Ever since Rokitansky's initial conclusion that atherosclerotic changes were the result of vascular organization of mural thrombi controversy has raged. At present, the basic process seems pretty well agreed upon, but this concession has come at the expense of a bewilderingly complex array of “contributing factors” and “predisposing causes”.

Basically, the process of atherosclerotic degeneration is one of incorporation of foreign materials, chiefly lipids, into the arterial wall, and a resultant series of reactive changes resulting in loss of flexibility, thickening, and fibrotic and calcific hardening. These events are accompanied by changes in the vessel wall enzyme systems and altered platelet agglutination reactions at a local and perhaps as well at a systemic level. The exact nature and causal implications of the latter two factors are under

investigation at present and deserve some amplification here. Zemlenyi² reports that diseased segments of arterial wall reveal a decreased activity in the krebs oxidation cycle enzymes with a concurrent increase in phosphoric hydrolase and related enzymes. Furthermore, these changes are progressive, and seem to be dependent on some exogenous factors rather than being inborn. Significantly, all such age-linked alterations appear to depend on the quantity and quality of local smooth-muscle cells, whose metabolic activity declines quite clearly following vascular injury. It seems such damaged tissue begins to depend more and more on glycolysis, resulting in decreased phospholipid synthesis and a consequent impairment of transport and solubilization of "sclerogenic" lipids and cholesterol.

Similarly related to the topic of vascular injury, Mustard, Rowsell, Murphy and Downie³ showed experimentally that platelet clumping may take place at a concentration of thrombin below that which produces fibrin deposits. Intimal damage with resultant exposure of collagen fibres and the appearance of positive charges that attract the negatively charged platelets may be responsible. In addition, local release of adenosine triphosphate and diphosphate after damage of red blood cells and platelets enhances both platelet agglutination and plasma lipid incorporation by arterial intimal cells.

Two further processes in the course of ASHD are often neglected. Hemorrhage can often be the precipitating event in a case of coronary thrombosis, and as well may be present in less crucial degrees throughout the process of elastic and medial deterioration thus leading to the further progression of the atherosclerotic process. Secondly, atheroembolism, the release of fragmentary portions of the atherosclerotic plaque into the circulation, does occur, as shown by the finding of cholesterol crystals and associated debris in target tissues. As such, this phenomenon may play an important role in sudden onset small vessel ischaemia, as well as coronary insufficiency and infarction.

Let us now turn away from the microscopic aspect and discuss the myriads of additional factors and figures which are assumed to play a role in the pathogenesis of ASHD. Epidemiologically, many studies have confirmed a general link between the intake of foodstuffs rich in fat from animal sources and the overall incidence of ASHD and generalized atherosclerosis. There is a high positive correlation, moreover, between the percent of calories from saturated fat and the death rate, and a low correlation between the percent of calories derived from polyunsaturated fats and the death rate.

In animal experiments, dietary fat and cholesterol are the essential prerequisites for the development of atherosclerotic-like lesions. In man, chiefly from the results of epidemiologic data, it seems reasonably safe to say that with rare exceptions, life-long dietary habits established on a society-wide level are of prime importance in the

development of ASHD. In animals, atherosclerosis is not caused by an excessive synthesis of cholesterol but follows excessive dietary intake of cholesterol and fat. In the vast majority of patients with hypercholesterolemia and atherosclerosis, this probably is also true.

However, by no means should this be interpreted as saying that improper diet or altered serum lipids are the cause of atherosclerosis. It is accepted by all who are involved with this disease that multifactorial etiology is responsible. Various hereditary, individual, and environmental factors display a strong correlation to the morbidity and mortality of ASHD, among which dietary fats and serum cholesterol are prime examples. More about the importance of these parameters will be noted when therapy is discussed.

CONTRIBUTORY ETIOLOGICAL FACTORS

SEX

Now, don't jump to conclusions. What we are discussing here is the almost complete immunity of females in the reproductive years to ASHD. The incidence in females rises sharply in the years following the menopause. Exactly why this should be so is unknown. Mustard⁴ et al. have demonstrated cyclic changes in blood coagulation and platelets, and also that the blood from women immediately before menstruation reacts negatively in the thromboplastin generation test. Such findings are even more topical in light of the association of hormonal therapy in women and a postulated increased incidence of thromboembolic phenomena.

OBESITY

Surprisingly, on an individual level, there is no clear cut relationship between obesity and ASHD. The correlation attempts are complicated by the considerations that hypertension, atherosclerosis and obesity are all age-linked and commonly associated with each other in our society. No significant relation between subcutaneous fat thickness and the incidence of ASHD has been found. On a national level, however, in countries with wide economic variations and consequent wide dietary variations from starvation to obesity, there is a marked correlation between body fat and serum cholesterol. In countries where food is generally abundant, such as Canada, no such correlation is found. The probability is that Canada's average is abnormal from the point of view of atherogenesis.

HYPERTENSION

In health, the risk of subsequent development of ASHD rises steadily as the pressure rises *throughout* the normal and abnormal ranges. There is no critical point above which there is a sharp increase. Furthermore, this holds true at various levels of serum cholesterol, and there is no significant correlation between blood pressure and cholesterol.

ATHEROSCLEROSIS: AN ETIOLOGIC AND THERAPEUTIC REVIEW

Apparently in man, as in the experimental animal, hypertension by itself does not lead to atherosclerosis, but in the presence of a substantial level of serum cholesterol hypertension will accelerate and aggravate atherogenesis.

PHYSICAL ACTIVITY

There is no clear cut evidence to suggest that physical exercise is prophylactic against ASHD. For wide groups of patients, those with clinically evident disease did not differ significantly in life-long exercise pattern from those who were free of ASHD.

Experimental evidence in animals has shown that better collateral circulation can be induced in cases of arterial narrowing by programmed exercise, although this has yet to be proved in man.

NICOTINE

Cigarette smokers develop more ASHD in the form of myocardial infarction or sudden death, but not angina. Significantly, pipe and cigar smokers are not involved. Furthermore, the risk of ASHD rapidly approaches normal when smoking is stopped. Rather than actually enhancing or contributing to the atherosclerotic process, nicotine probably acts on myocardial irritability and sensitivity to ischaemia.

THERAPY

Essentially, atherosclerotic heart disease is a complex and poorly understood epidemic of today. The bulk of experimental and epidemiological evidence shows that certain subgroups of our society deserve active therapeutic attempts based on current knowledge in an effort to reduce morbidity and mortality.

The therapeutic problem may be best stated as; what? when? who? and how? do we treat.

WHAT?

In the absence of thrombotic complications coronary atherosclerosis might more frequently remain asymptomatic throughout a normal lifespan; yet without atherosclerosis thrombosis in the coronary arteries probably would never occur. Therefore to treat the primary problem we must treat atherosclerosis itself rather than complicating factors or effects.

WHEN?

There are no definitive data which prove that any known method be it dietary, medical or surgical will prevent, postpone or reverse atherosclerosis in the human. Yet indirect evidence does exist that atherosclerosis is preventable and within limits reversible in the human. For example post mortem studies of people dying of wasting diseases such as cancer or starvation have revealed a substantial decrease in atherosclerosis. Men with prostatic cancer treated with estrogens show less atherosclerosis than those not so treated. Obviously reversibility of the disease applies particularly, if not solely, to the early phase of the disease where the fatty element is pre-

dominant, rather than to the late stage where fibrotic and calcific changes have occurred. Unfortunately only advanced, occlusive disease can be diagnosed in the living patient.

Therefore treatment, be it drug or dietary, is either prophylactic and directed to apparently healthy populations or individuals characterized as prone to ASHD, or therapeutic, directed to individuals who already have ASHD, in an effort to prevent further morbidity and mortality.

WHO?

It is statistically valid to consider that patients with moderate hypercholesterolemia (i.e. a plasma cholesterol level between 250 and 350 mgm/100 ml.) are subject to three to five times a greater risk of developing vascular accidents than normocholesteremic subjects in any five year period.

"A patient having a persistent plasma cholesterol level greater than 500 mgm/100 ml might justly be considered as seriously ill as a patient harbouring a malignant neoplasm."⁵

It has been suggested, although not proved, that a 15 to 20% reduction in the level of an elevated blood cholesterol level will reduce the incidence of myocardial infarct by 20-30%. If true this would mean a reduction in the total mortality in the U.S. of approximately 100,000 persons or more per year.

Of all factors leading to ASHD the greatest contribution is made by the serum cholesterol levels. Familial or essential hypercholesterolemia is associated with the appearance of premature atherosclerotic heart disease. Yet lowering the serum cholesterol of post infarct male patients did not necessarily prolong life. Therefore lowering serum cholesterol levels of healthy groups and individuals might reasonably be expected to prevent or at least postpone ASHD, but once the disease is clinically manifest it may be of little value.

Our society as a whole can be classed as a high risk group for ASHD and certain groups mentioned in the preceding section are especially prone. In these special high risk groups, at least, it would be wise to prescribe prophylactic diets in the hopes of decreasing mortality and morbidity. The time to act is before the infarct.

Treatment of certain high risk groups can be effective simply by removing the special high risk factors (i.e. treatment of hypertension, especially in younger men; the close control of diabetes; the lowering of serum uric acid levels preferably by sulfinpyrazone (Anturan)) which also decreases platelet stickiness in gouty subjects or even in healthy ones; the treatment of hypothyroidism and premature female castration.

All high risk individuals should be put on altered fat diets. Those with hypercholesterolemia or hypertriglyceridemia will require special efforts. Their altered fat

diets must be constructed as rigidly and with the same limitations as diabetic diets with the amount and kinds of foods specified and rigidly controlled.

How?

A. Diet

As noted before, populations characterized by overweight and obesity as well as those characterized by high serum cholesterol levels have a higher incidence of ASHD. The frequency of high blood pressure and the fact that both obesity and atherosclerosis tend to increase with age also complicates the picture. But we can say that on the average, weights in North America are far from ideal with respect to atherogenesis. To reduce ASHD associated with obesity we would have to greatly reduce the average weight of our adult population—a practical impossibility.

An anti-atherosclerosis diet requires reduction in levels of saturated fat and cholesterol as well as moderate restrictions in fat and calories. As little as 475 mgm of dietary cholesterol, equivalent to 2 egg yolks, can greatly increase the serum cholesterol levels. Natural food products such as vegetables, oils, fruits, cereals and nuts should be stressed. Such a diet might allow some 1800 - 2500 calories of which 50% would be carbohydrate and 25% each of protein and fat. Less than half the fat would be saturated and the cholesterol intake would be restricted to about 200 mgms. per day. With this type of diet the fall in serum cholesterol averages about 15% but the range is wide with the greatest reductions occurring in those with the highest pretreatment levels.

This diet will also favourably influence blood coagulation, platelet survival and fibrinolysis in a direction possibly protective against thrombogenesis and the thrombotic complications of atherosclerosis.

Since the change in dietary pattern must be permanent, the recommended diets must be made up of ordinary foodstuffs. The principle reduction of fat must come from the two main food groups that contribute most of the saturated fat:

1. Milk fat—whole milk, cream, cheese, butter etc.
2. Meats—only limited amounts of lean meat and fowl are allowed. Egg yolks are eliminated.

The vegetable oils, rich sources of linoleic acid, are used extensively in baking and frying, in salad dressings etc. Nuts, especially almonds and walnuts are also recommended as are most fish. Now available is a wide variety of low calorie, low fat foods and unsaturated products such as vegetable ice cream and whippings. As well as diet, the dangers of cigarette smoking must be emphasized.

Even in post-infarction patients, a no-saturated fats diet, particularly avoiding egg yolk and milk, is beneficial in that it may alter the coagulation fibrinolysis mechanisms so as to decrease the incidence of coronary

thrombosis. In many patients treated in hospital after an infarct, such a diet combined with a restricted salt intake is standard.

B. Drug Therapy

Therapy is directed generally towards lowering blood cholesterol levels by the following means:

- i) Inhibit Cholesterol Synthesis: eg. CPIB (Atromid-S), Nicotinic Acid.
- ii) Inhibit Gastrointestinal Absorption: eg. cholestyramine, neomycin, sitosterol.
- iii) Increase Cholesterol Excretion: eg. dextro-thyroxine (D-T₄).

It is well known that the menstruating female is almost immune to ASHD. It is therefore reasonable to offer estrogen to the castrated female to prevent the increased ASHD which they experience. Whether this will affect the post menopausal female remains to be seen. The use of estrogens in males has so far had conflicting results and although the use of natural estrogens does seem to have some beneficial effects, side effects are troublesome.

- (i) Inhibit Cholesterol Synthesis
e.g. Clofibrate (Atromid-S)

Patients with hyperlipemic states involving elevation of both serum triglycerides and serum cholesterol generally have a more favorable response than those with primary hypercholesterolemia with normal triglyceride levels.

Atromid-S remains almost exclusively in the blood, a high concentration of the free acid being bound to plasma proteins. Presumably, the clofibrate anion competes with other anions, including androgens and thyroxine for the same binding sites in the plasma proteins. These displaced substances are transferred preferentially to the liver and their combined effects influence lipid metabolism by decreasing lipid synthesis and indirectly, serum lipids. As far as is known, there are no toxic metabolites accumulating in the serum as was the case with MER-29 (Triparanol).

After oral administration there is an average half life of 12 hours. It appears in the urine as the glucuronide conjugate. It is administered orally to adults in dosages of 500 mgm, b.i.d. or q.i.d. As of yet, no teratogenic effects are known, but in the rabbit, abnormal amounts of the drug accumulate in the fetus. It is not recommended for pregnant, soon to be pregnant or lactating women. It is also not recommended for those with impaired renal or hepatic function.

Adverse Reactions: nausea, vomiting, loose stools, dyspepsia, flatulence, and abdominal distress, headache, dizziness, fatigue, weakness, skin rash and urticaria may occur.

Caution should be exercised when anticoagulants are given in conjunction with Atromid-S. The dosage of the anticoagulant should be reduced by one third to one-half

(depending on the individual case) to maintain the prothrombin time at the desired level. Frequent prothrombin determinations are advisable until it has been definitely determined that the levels have stabilized.

If after three months the serum lipid response is inadequate the drug should be withdrawn. SGOT levels should be done during the early stage of administration. Mild transient increases do occur but if excessive abnormalities occur the drug should be withdrawn. The effect of Atromid-S is consistent and sustained. After continuous treatment, when the drug is withdrawn, serum lipids often rise within two to three weeks up to or above pretreatment levels.

(ii) Inhibit G.I. Absorption Cholestyramine

Cholestyramine resin is a non-absorbable anion exchange resin which releases chloride ions in the intestine and binds bile acids. Since these bound bile acids cannot re-enter the enterohepatic circulation, and since the rate at which hepatic cholesterol is converted to bile acids is controlled in part by the concentration of the bile acids reaching the liver at any time, then the hepatic rate of cholesterol oxidation to form bile acids is increased and blood cholesterol levels drop. It is also used in the treatment of pruritus associated with incomplete biliary obstruction.

The medication is taken in four equal doses after each meal and at bedtime for a total of 13.3 gms/day p.o. It produces a fall of from 20-50% in serum total cholesterol levels and this drop is maintained during the duration of treatment. On termination of treatment the bile acid excretion rate returns promptly to pretreatment values as does the serum cholesterol level.

There is little or no increase in neutral sterol excretion during cholestyramine administration. In general the cholestyramine is well tolerated. Once ingested the preparation produces occasional G.I. discomfort, ranging from slight distension to peptic distress. Such symptoms, more frequent during early treatment, tend to disappear after the first few weeks of resin therapy. Constipation is common and is usually controllable by adjustment of the fibre content of the diet. Systemic side effects are not encountered although it is thought that large doses of Cholestyramine resin (30 gm/day) can induce mild to moderate malabsorption in normal human subjects.

(iii) Increase Cholesterol Excretion Sodium Dextro-Thyroxine

In man myocardial infarction is rare in hyperthyroidism, but hypothyroidism is often associated with hyperlipidemia and probably with premature ASHD. Thus thyroid analogues are being used in the treatment of hypercholesterolemia, hyperlipemia and ASHD. It is also used in cases of tuberous xanthomas where the xanthomas are seen to markedly decrease during therapy. Gener-

ally it acts to lower cholesterol levels by 20 to 35% although the higher the pretreatment levels the greater the fall in serum cholesterol levels.

Administered orally it is absorbed into the blood from the G.I. tract and it appears to stimulate the liver to increase catabolism and the excretion of cholesterol and its degradation products via the biliary route. It is therefore claimed that cholesterol synthesis is not inhibited and abnormal end products do not accumulate in the blood.

Generally there is a dramatic cholesterol reduction during the first three months of therapy and this lowered level of serum cholesterol is maintained on constant D-thyroxine therapy. Contraindications: acute myocardial infarct, uncontrolled atrial fibrillation, decompensated cardiac status, cardiac hyperirritability, history of iodism, pregnancy and nursing. Warning is required for use in diabetics since blood sugar is increased in some patients requiring adjustment of their therapeutic regimen. The effect of oral anticoagulants on prothrombin time and factors VII, VIII, IX and platelet activity may be enhanced, requiring adjustment of anticoagulant drug dosage. Potentiation of catecholamines may occur, sensitizing the myocardium to arrhythmias or ischemia. Hypothyroid patients are more sensitive to thyroid medications than are normals. Greatly increased PBI values are evidence of absorption and transport of the drug and should not be interpreted as evidence of hypermetabolism. PBI values in the range of 10-25 mg% are common.

Adverse Reactions: (due for the most part to metabolic stimulation) Increased angina has been reported in a small percentage of patients but reported improved in others. Arrhythmias have been reported in 0.6% and myocardial infarctions in 1%. Insomnia, palpitations, tremors and nervousness have also been reported in 1 to 2.5%. Also insomnia, tremors, weight loss, sweating, hyperthermia, increased appetite, G.I. complaints etc. have all been reported but the withdrawal rate has been less than 5%.

Dosage: Patients with coronary artery disease should start at 1.0 mg daily and be increased monthly in 1.0 mg increments until a maintenance dose of 4.0 or 6.0 mg daily is reached. In other patients the initial daily dose should be 2.0 mg to be increased monthly in 2.0 mg increments to a maximum of 8.0 mg daily.

After patients are on therapy four or five weeks they often develop a feeling of well-being and a decrease in weariness.

CONCLUSION

In this article, we have discussed at some length the current thoughts with regard to the etiology and therapy of atherosclerotic heart disease. It is our view that a more aggressive approach to the treatment of atherosclerosis is warranted than is currently the practice among most medical centres. The medical therapy of ASHD

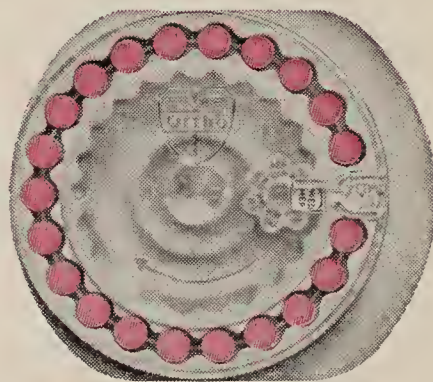


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must be primarily prophylactic and directed to high risk groups or young post-infarct patients. It must be complete and rigidly controlled, consisting of:

- Diet
- Cessation of cigarette smoking
- Drug therapy if necessary

The most useful parameters in assessing the efficacy of (a) and (c) are at present serum cholesterol and serum triglyceride levels.

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Primary Mechanisms Of Maintaining Cardiac Reserve

G. Skrinskas TT0

CONCEPT OF CARDIAC RESERVE

Normal cardiac function is characterized by a variability of performance which is remarkably adapted to changing demands. In health and disease, the heart is potentially capable of a wide range of increased work performance above that required under basal conditions. Cardiac reserve is defined as the difference between the existing performance and the maximal effort of which it is capable. The reduction in cardiac reserve is the first step on the pathway to cardiac failure and the severity of cardiac disability is measured by the degree of impairment of this excess pumping capability.

A number of cardiovascular compensatory mechanisms serve to restore an adequate cardiac output and maintain cardiac reserve whenever these are threatened by disease in any part of the system. The primary compensations concern the heart directly and include tachycardia, cardiac dilatation and cardiac hypertrophy. The augmentation of cardiac performance of these mechanisms is achieved through the operation of Frank-Starling's Law of the Heart and the adjustments effected by the autonomic nervous system. They serve to alter the two broad general properties of heart muscle—a change in initial muscle length and a change in the contractile state of the heart.

It must be emphasized, that although the compensatory mechanisms tend to restore the cardiac reserve to normal, they can never achieve this goal completely because each mechanism demands extra work from the myocardium—work capability that under normal circumstances would make up part of the excess pumping capacity.

FRANK-STARLING LAW OF THE HEART

The observation that within physiologic limits a larger diastolic cardiac volume results in a greater energy of contraction and a greater amount of chemical change at each contraction has been termed the Frank-Starling Law of the Heart. The major determinants of ventricular end-diastolic volume and therefore myocardial fiber length in the intact organism are total blood volume, distribution of blood volume according to body position, intrathoracic pressure, intrapericardial pressure, venous tone, the pumping action of skeletal muscle, and atrial contribution to ventricular filling.

At the present time, the major features of the ultrastructural basis of Starling's Law have been elucidated.

The sarcomere is the fundamental structural and functional unit of contraction. It is delimited by two adjacent dark lines, Z lines, seen with the electron microscope and under physiologic conditions the distance between Z lines measures from 1.5μ to 2.5μ , depending on overall muscle length. The contractile system of the sarcomere is composed of two sets of actin and myosin filaments arranged in a partially overlapping array, with the thinner actin filaments fixed in the Z line. In the sliding filament mechanism, the actin and myosin filaments interact without change in overall length; adenosine triphosphate (ATP) is split and directional forces are generated between these two filaments, with resultant shortening. The combination of actin and myosin at reactive sites triggers a magnesium-activated ATPase, which also requires trace amounts of calcium, and linkages are made and broken cyclically. The small amounts of calcium that regulate this reaction are thought to be released and reaccumulated by the longitudinal portion of the sarcoplasmic reticulum in response to depolarization. During contraction, ATP serves as the immediate source of energy, its rate of breakdown being proportional to the work performed during contraction. In addition, if the ATPase activity of actomyosin is inhibited, as occurs in the absence of calcium, ATP is required to keep actin and myosin separated.

In all forms of striated muscle, the force of contraction depends on initial muscle length and sarcomere length is directly proportional to muscle length. The relation between sarcomere length, muscle length and the relative tension developed is shown in Fig. 1. At $L(\max)$, the sarcomeres measure 2.2μ and at this length the two sets of myofilaments are most ideally situated to provide the greatest area for their interaction. Considering that the central 0.15μ to 0.20μ of the thick myosin filament is devoid of reactive sites, the force of contraction remains about maximal between sarcomere lengths of 2.0μ and 2.2μ . When the sarcomere shortens to less than 2.0μ , the passage of actin filaments through the centre of the sarcomere disrupts some of the bonds leading to a decrease in the number of reactive sites between the filaments, causing a reduction of developed tension. When the muscle is stretched beyond optimal length, the sarcomere is stretched beyond 2.2μ and the thin actin filaments are partially disengaged from the thick myosin filaments. Force development falls in direct proportion to the decrease in overlap with the resultant decrease in the number of adjacent reactive sites. Unlike skeletal muscle, there is no linear relation between muscle length and sarcomere length in heart muscle which is overstretched

PRIMARY MECHANISMS OF MAINTAINING CARDIAC RESERVE

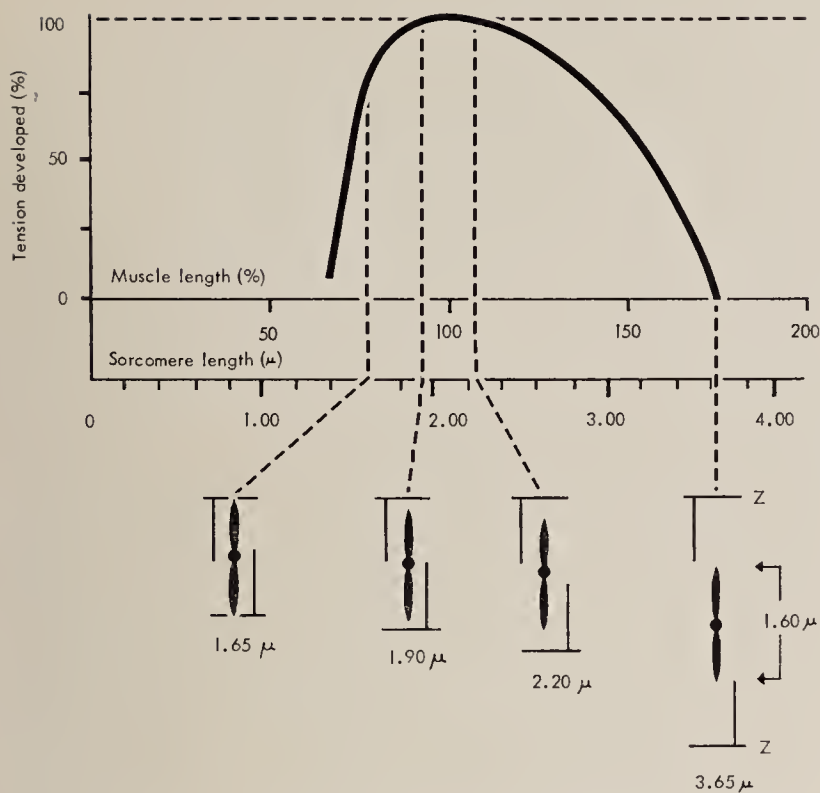


FIG. 1. Relation between Sarcomere Length and Relative Tension Development for Single Myocardial Fiber. The extent of thick and thin filament overlap in relation to developed tension is shown.

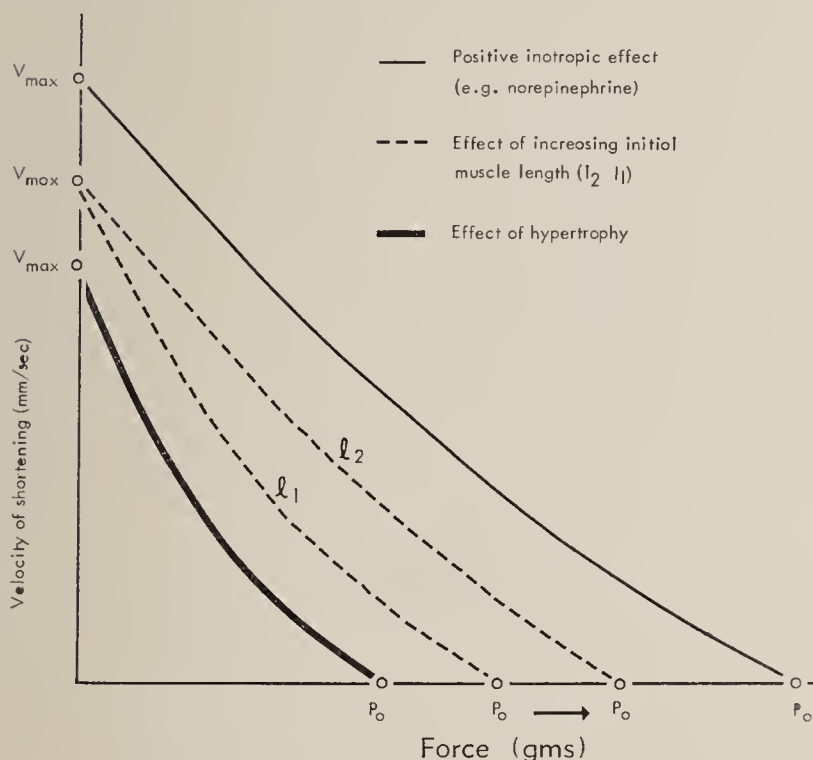


FIG. 2. Effects of positive inotropic agents, initial muscle length and hypertrophy on Force-Velocity Relation of Isolated Cardiac Muscle.

along the descending limb of the length-active tension curve. In cardiac muscle, it appears that there must be slippage of the individual muscle cells at this degree of stretch. In general then, an increase in initial muscle length may be thought of bringing about a rise in the number of force-generating sites operating within the sarcomere without a change in the qualitative character of the cyclic process occurring at these contractile sites. The sarcomere length-active tension curve forms the ultrastructural basis of Starling's Law of the heart.

FORCE-VELOCITY RELATION OF MYOCARDIAL CONTRACTION

The Frank-Starling mechanism can also be represented as a force-velocity relation (Fig. 2). The effect of increasing initial muscle length is to augment the maximum force of contraction (P_o), whereas the maximum velocity of shortening $V(\max)$ is essentially unchanged.

On the other hand, a change in the contractile state of the myocardium can be brought about by positive inotropic intervention. It is characterized by an increase in $V(\max)$ resulting from a fundamental alteration in the cyclic force-generating processes at each contractile site, with or without an increase in the number of sites. A number of sympathomimetic amines, norepinephrine, epinephrine, mephentermine, and metaraminol, various cardiac glycosides and a simple increase in heart rate stimulate the force of ventricular contraction and displace the force-velocity relation upward and to the right (Fig. 2). The total ventricular performance at any given level of end-diastolic volume is depressed in the presence of physiologic depressants, eg. myocardial hypoxia, hypercapnea, acidosis, pharmacologic depressants, eg. quinidine, procaine amide, barbiturates, loss of ventricular substance as occurs in myocardial infarction, and in the presence of intrinsic myocardial depression as occurs in heart failure.

TACHYCARDIA

As a rule, tachycardia appears only as a transient compensatory mechanism, especially with a sudden increase in cardiac demand. However, when stroke volume cannot be increased either because of severe acute myocardial injury or because of a sharply reduced blood volume and venous return, tachycardia becomes a major compensatory mechanism.

The increase in heart rate is effected by various mechanical, chemical and nervous stimuli acting at the vasomotor centre to diminish the tone of the inhibitory centre and vagus nerve and, more important, to increase the tone of the cardioaccelerator centres and fibers in the sympathetic nervous system. Nerve endings within the myocardium contain large quantities of norepinephrine that can be released by nerve stimulation causing increased rate of tension development, elevation of maximum isovolumic tension, and tachycardia. An intrinsic mechanism operating by stretching the S-A nodal fibers due to increased atrial filling is also believed to effect an increase in heart rate. The positive inotropic agents (tachycardia and sympathetic nerve activity) shorten the relative duration of systole, providing the ventricle with a relatively longer diastolic filling period and a decrease in end-diastolic dimensions.

The compensatory value of tachycardia reaches its upper limit at about 160 beats per minute, when diastole becomes shortened enough to encroach upon the rapid inflow phase of the heart cycle and the consequent de-

crease in ventricular filling. At high heart rates, the oxygen supply to the myocardium is inadequate to meet the increased metabolic requirements, since the major blood flow through the myocardium, especially the left ventricle, occurs during diastole. In addition, the long term presence of tachycardia is accompanied by depletion of cardiac norepinephrine stores, so that the quantity of neurotransmitter released by the sympathetic nerve endings is diminished in relation to the impulse traffic along these nerves. This is responsible for the loss of the much needed adrenergic support to the already overworked heart and the cardiac reserve falls.

CARDIAC DILATATION

Cardiac dilatation denotes an increase in the capacity of the cardiac chambers. It may result from mechanical lesions that tend to increase diastolic volume by a) an increase in venous return, eg. A-V shunting, anemia or thyrotoxicosis; b) increase in resistance to outflow from one of the chambers, eg. mitral or aortic valvular stenosis, or hypertension; c) by permitting a reflux of blood into a chamber after ejection, eg. aortic valve insufficiency. Dilatation may also result from myocardial lesions that tend to impair cardiac contraction although the inflow is temporarily unchanged, eg. myocardial infarction or rheumatic myocarditis. In general, dilatation results from an inability of the affected chamber to expel an increased venous return or to eject normal venous return against an abnormal obstruction or a regurgitant stream.

The compensatory action of dilatation is explained by the Frank-Starling Law of the Heart. There is an increased stroke output as well as a lesser degree of shortening per muscle fiber required to eject a given volume of blood during systole than in the normal heart.

On the other hand, in the dilated heart the diastolic volume and the residual volume are increased, so that it must support a greater load throughout the cycle. The increase in chamber radius (R) also places the dilated heart at a disadvantage in that it must develop a higher wall tension (T) to produce an equivalent cavity pressure (P) during ejection (Laplace's Law: $P = T/R$). It also demands increased metabolic requirements for production of the contractile force at increased fiber lengths.

If a moderate degree of cardiac dilatation effects the needed increase in cardiac reserve, this remains unchanged so long as the status of the mechanical and myocardial lesions remains unchanged. When the increased strength of contraction set free by the increased fiber length due to dilatation is no longer able to compensate for the disadvantages of increased metabolism, increased load, greater wall tension as well as the original mechanical or myocardial lesion, then this mechanism fails in restoring adequate cardiac reserve and cardiac output. The heart, however, continues to dilate in a futile compensatory effort and progresses on the downward limb of the length-active tension curve.

CARDIAC HYPERTROPHY

Cardiac hypertrophy denotes an increase in weight of the heart associated with an enlargement in the diameter and volume of the individual myocardial fibers. This applies to hearts which are hypertrophied to a total weight of 500 gms. Beyond this point, the fibers may split longitudinally and produce an increase in the number of fibers as well. The increased size of the fibers is associated with an increase in total RNA and an increase in the ratio of RNA to DNA. As expected, the protein synthesis pathways are intimately involved in hypertrophy.

Many theories have been advanced to explain the development of hypertrophy. 1—The theory of "work hypertrophy" attributes cardiac hypertrophy to an increase in work of the heart, perhaps through an increase in the oxygen consumption per beat, as the stimulus. 2—The "nutritional" or "hypoxic" theory suggests a defective blood supply with prolonged intermittent exposure to hypoxia as the stimulus. 3—The "injury" theory suggests hypertrophy is a reaction to tissue injury which acts as a pathologic nutritive stimulus. 4—The "muscular stretch" theory suggests that the fundamental cause of hypertrophy is stretching of the fibers resulting from dilatation. The constant increase in length of the fiber may be relayed in some way to the nuclear material of the cell, leading to increased RNA and protein synthesis; the greater surface area available for diffusion of metabolites may also stimulate the fiber growth. Hormonal factors may be involved in any one of the above theories. However, at the present time, the exact stimulus and control of hypertrophy at the cellular level is not known.

That cardiac hypertrophy is a compensatory mechanism is concluded from experimental, pathological and clinical observations that: 1—it appears when there is a disturbance which tends to interfere with normal cardiac function; 2—it is localized in the chamber or chambers affected by the disturbance; 3—after its development, cardiac function is improved. Cardiac hypertrophy and dilatation are both compensatory mechanisms responding to the same mechanical or myocardial lesions; dilatation occurring immediately and hypertrophy after some time. Thus, hypertrophy may be a more efficient long-term compensatory response, but requiring more time to develop. In any particular case, the degree of predominance of one mechanism over the other varies depending upon the type of stimulus and its time course. As a rule, dilatation is the response to increased volume load, eg. valvular regurgitation, A-V shunt, whereas hypertrophy is the more prominent response to an increased resistance, eg. aortic stenosis.

The result of hypertrophy is to cause a change in the ultrastructure and metabolism of the myocardial fiber, as evidenced by elongated mitochondria with a disordered arrangement of cristae, the decline in the oxidative and phosphorylative power of the mitochondria, increased oxygen and other nutrient consumption. The normal

hexagonal-lattice geometry of the myofilaments is maintained and sarcomere length is not increased in pure hypertrophy, but the characteristics of fiber contraction are altered. There is a reduced maximum velocity of shortening as well as a depressed maximum developed tension. Although hypertrophy is associated with a depression of the contractile state of the unit myocardial fiber, the absolute increase in total muscle mass maintains cardiac compensation.

The limit of this compensatory mechanism is reached when the blood supply becomes inadequate to meet the increased demands of the myocardium. Throughout life in the adult, the capillary to myocardial fiber ratio is 1:1. This relationship is maintained in the hypertrophied heart, so that the capillary surface area per unit mass of heart muscle decreases and the diffusion distance increases. When the absolute increase in contractile force is unable to be maintained by sufficient nutrient supply to the hypertrophied fibers, the cardiac pumping capacity decreases.

Roentgenologic observations have disclosed that cardiac enlargement (dilatation and hypertrophy) are reversible, at least partially, even when it has been present for years, provided that the causative disturbance is abolished or alleviated by surgical or medical measures.

CARDIAC PERFORMANCE

The extent of shortening of the myocardial fiber, and therefore the stroke volume of the intact ventricle, is, in the final analysis, determined by three influences: the length of the muscle at the onset of contraction, as determined by the ventricular end-diastolic volume; the ten-

sion that the muscle is called upon to develop during contraction, as influenced by the peripheral vascular resistance, the physical characteristics of the arterial tree and the volume of blood that it contains at the onset of ejection; and the contractile state of the muscle, that is, the position of its force-velocity-length curve.

The normal cardiac output of about 5 litres per minute in the average adult can be increased up to 5 to 6 times this control value in the young, well-trained athlete. The average normal adult heart has a reserve of 300 to 400 percent. Almost any pathologic condition decreases cardiac reserve and, in the mildest cases, a falling cardiac output is adjusted by cardiac dilatation and hypertrophy, and, if unsuccessful, by tachycardia as well. Although beneficial in their effect on cardiac output, they are abnormal in that they denote the existence of a serious disease which requires cardiac compensation; they expend some of the reserve pumping capability of the heart and demand increased nutrient supply. Thus, cardiac enlargement and tachycardia may be considered as compensatory processes, as evidence of cardiovascular disease and as predisposing factors to heart failure.

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Drug Treatment Of Cardiac Arrhythmias

D. Butcher 6T9

Ever since physicians first listened to the heart with only their ear placed on the chest, disorders of beat have been associated with grave consequences.

Our methods of examining the heart have improved and now include such machines as the ECG and the phonocardi-recorder. These instruments allow us not only to hear the heart sounds, but also to record and see the pattern of the heart beat.

Disorders of heart rhythm are all variations from the normal sinus rhythm. Normally the S-A node in the right atrium is responsible for initiating the electrical impulses which result in myocardial depolarization. If there is an arrhythmia it often indicates that another focus in the myocardium has partially or completely taken over control from the S-A node. These ectopic foci may arise in either atrium, in the conducting fibers of the heart, A-V

node, bundle of His, Right or Left bundle, or in the ventricular myocardium. Wherever the new pacemaker arises it behoves the physician to determine the type of rhythm present and to take steps to return the normal sinus rhythm. It is the purpose of this article to present some of the common arrhythmias encountered in practice, and to show how they are best managed.

What causes a change from the normal sinus rhythm? These changes can occur in patients with no detectable structural heart disease. The cause in these cases usually remains a mystery. Included among the arrhythmias in this category are: sinus arrhythmia, sinus bradycardia, sinus tachycardia, atrial and ventricular premature beats, and mild first degree heart block.

Arrhythmias also occur in those with organic heart disease. These include fibrillation and tachycardia of the

ventricles, atrial flutter and fibrillation. Auricular fibrillation is seen in elderly patients, in those with mitral stenosis and thyrotoxicosis. Patients with coronary disease have ventricular tachycardia more often than those with no coronary disease.

These are also drug induced arrhythmias such as those caused by digitalis or quinidine toxicity.

Arrhythmias may be classified as follows:

I. Supraventricular

II. Ventricular

Supraventricular is further sub-divided:

A. in the S.A. Node:

- (i) sinus bradycardia
- (ii) S-A block
- (iii) Sinus arrhythmia
- (iv) Sinus tachycardia

B. in Atria:

- (i) Atrial premature beats
- (ii) PAT (paroxysmal atrial tachycardia)
- (iii) PAT with block
- (iv) Atrial flutter
- (v) Atrial fibrillation

C. in A-V Node:

- (i) Ectopic Nodal beats—high in node
—low in node
- (ii) Nodal tachycardia
- (iii) Nodal bradycardia

Ventricular arrhythmias include:

- (i) VPB (ventricular premature beats)
- (ii) Ventricular fibrillation
- (iii) Ventricular tachycardia

There are also disturbances in the conducting system of the heart which lead to arrhythmias. These include: first degree (prolonged P.R. interval, > 0.2 sec.), second degree (dropped ventricular beats), and complete heart block (ventricles beat at own inherent rhythm).

Not all of the arrhythmias listed require treatment. Those most commonly treated include: atrial fibrillation and flutter, supraventricular tachycardia, ventricular premature contractions and ventricular tachycardia.

In a study done in 1964 the incidence of these arrhythmias was recorded after myocardial infarction. The results were as follows:

Ventricular Premature contractions	— 82%
Ventricular tachycardia	— 50%
Atrial fibrillations, flutter	— 10%
Supraventricular tachycardia	— 3.3%

Five commonly used pharmacological agents used in treatment of these arrhythmias will be presented. These agents are Digitalis, Diphenyl-hydantoin, Lidocaine, Procaine Amide, and Quinidine.

DIGITALIS

Digitalis has long been one of the mainstays in the treatment of cardiac arrhythmias. The main problem in

using digitalis or one of its analogues is that it can precipitate as many arrhythmias as it combats.

The digitalis may be used either orally or intravenously. For rapid action intravenous administration is employed. If there is no emergency then p.o. medication is suitable.

For oral use, digoxin 0.75 - 1.0 mg initially followed by 0.25 - 0.5 mg in 60 - 90 minutes is suitable. Cedilanid 0.4 - 0.8 mg I.V. over 2 - 3 minutes followed by 0.4 mgm 60 - 90 minutes later is advocated for rapid digitalization. At all times one must be aware of the patient's previous digitalis status.

Digitalis is useful in treatment of: Paroxysmal atrial tachycardia, paroxysmal atrial tachycardia with block (if digitalis is not the cause), atrial fibrillation and atrial flutter.

The mechanism of action of digitalis involves the slowing of ventricular rate primarily as a result of circulatory improvement resulting from beneficial effects on the myocardium. There is some slowing of heart rate from a direct vagal action. Also, digitalis works on the A-V node to increase the refractory period and slow the conduction rate.

The side effects are due mainly to excessive dosage. These effects include anorexia, nausea, vomiting, malaise, blurred vision, lassitude, disorientation. Cardiac side effects include all arrhythmias and conduction defects.

If it is not responsible for the arrhythmia, digitalis is one of the best drugs for treating arrhythmias; with the exception of conduction defects since as pointed out digitalis depresses the conduction system.

DIPHENYLHYDANTOIN (DILANTIN)

Diphenylhydantoin belongs to the anti-epileptic group of drugs. It was first used as an anti-arrhythmic drug in 1950; the first success was in 1958.

This drug works by stimulating metabolic processes involved in the active extrusion of sodium from cells. It raises the membrane threshold and decreases the susceptibility to seizure activity, and this also serves to decrease the frequency of ectopic foci in the myocardium.

Diphenylhydantoin may be used orally in a dose of 200 - 400 mg/day, or by I.V. infusion. The dose is 250 mg in one to three minutes I.V. repeated in 5 - 10 minutes. At these dosages the effect is seen in 30 seconds to 4 minutes, and a duration of action up to 4 - 6 hours may be expected.

Diphenylhydantoin finds use against such arrhythmias as paroxysmal atrial tachycardia, P.A.T. with wandering pacemaker, ventricular bigeminy, multi-focal ventricular premature contractions.

The side effects resulting from administration of diphenylhydantoin include: inhibition of sinus node rhythmicity, depression of A-V conduction, ventricular fibrillation; rapid intravenous administration can give respiratory arrest; hypotension also occurs due to peripheral

DRUG TREATMENT OF CARDIAC ARRHYTHMIAS

DRUG	ROUTE/DOSE	INDICATIONS	CONTRA-INDICATIONS	SIDE EFFECTS
1. Digitalis	<i>Oral</i> —digoxin .75-1 mg stat .25-.5 mg in 60-90 min. <i>I.V.</i> Cedilanid .4-.8 mg in 2-3 min. .4 mg 60-90 min. later	PAT PAT with block Atrial fibrillation Atrial flutter	Digitalis idiosyncrasy Myocardial infarct without failure Angina pectoris Ventricular tachycardia (V.T.)	Anoroxia, Nausea, vomiting Malaise, Blurred vision, Lassitude, disorientation. All cardiac arrhythmias esp. PAT
2. Diphenylhydantoin (Dilantin)	<i>Oral</i> 200-400 gm/day <i>I.V.</i> 250 mg/1-3 min. repeat in 5-10 min.	PAT PAT—with wandering pacemaker Multifocal VPB's Ventricular bigeminy complex A-V rhythm.		1. Inhibition of Sinus Node rhythmicity. 2. Depress A-V conduction 3. Ventricular fibrillation 4. Respiratory arrest 5. Hypotension
3. Lidocaine (Xylocaine)	<i>I.V.</i> 1-2 mg/kg stat <i>or</i> 1-2 mg/min. up to 500 mg in 20 min.	VPB V.T.	Stokes-Adams Syndrome A-V dissociation slow nodal or idioventricular pacemaker	1. Continuous infusion leads to euphoria, muscular fasciculation, discomfort in breath- ing swallowing, talking, blurred or double vision. 2. High levels of appre- hension, disorientation, convulsion. 3. Severe overdose— Respiratory depression and cardiac arrest due to medullary depression.
4. Procaine Amide (Pronestyl)	<i>Oral</i> 1 gm stat .5-1 gm q. 6 hr. <i>I.M.</i> .5-1 gm q. 6 hr. <i>IV</i> .2-1 gm	Atrial Fibrillation Atrial Flutter VPB. V.T.	Hypersensitivity to the drug	1. Hypotension (with I.V. administration) 2. Anorexia, nausea, vomiting 3. Lupus-like syndrome 4. Agranulocytosis, arthralgia, eosinophilia.
5. Quinidine	<i>Oral</i> 200-400 mg q. 4-6 hr. Atrial fibrillation use: .2 gm q. 2 hr. x 5 increase each dose by .1 gm/day until reversion or toxicity occurs. Do not exceed 4 gm per day <i>I.V.</i> —only for life endangering arrhythmias	Atrial Arrhythmias (APB, Atrial fibrillation, Atrial tachycardia).	1. Quinine sensitivity 2. Partial or complete A-V block.	1. Diarrhea, nausea, vomiting 2. Respiratory paralysis and sudden death (rare) 3. Hypotension after parenteral administra- tion 4. Myocardial toxicity.

vasodilatation and decreased myocardial contractility. Skin rashes, drowsiness, depression or nervousness, arthralgias, gingival hypertrophy and transient eosinophilia are also encountered.

LIDOCAINE (XYLOCAINE)

Lidocaine or 2-diethylamine — 2',6' acetoxylidide is commonly used as a synthetic local anaesthetic. In 1950 it was found to have anti-arrhythmic properties. Today intravenous lidocaine is commonly used in the treatment of ventricular tachycardia following myocardial infarction.

The mechanism of action of lidocaine on the myocardium is not known. It is known that the drug decreases ventricular excitability, prolongs conduction time, and prolongs the refractory period. It does not decrease cardiac contractility nor decrease blood pressure.

For treatment of arrhythmias it is used exclusively by intravenous administration. The dosage suggested is 1 - 2 mgm/kg every 20 minutes to a maximum dose of 750 mgm/kg. A ventricular response is also used. This regimen works within 90 sec. to abolish ventricular extrasystoles.

Lidocaine is most useful in treatment of ventricular premature contractions and ventricular tachycardia. It has little, if any, effect on supraventricular arrhythmias.

The side effects of the drug depend on how the dose is given. With a 1 - 2 mgm/kg dose, only transient drowsiness results. From a continuous infusion, side effects include euphoria, muscular fasciculations, discomfort in breathing, swallowing, speaking, blurred or double vision, sensations of heat, cold, numbness, and sweating. With higher levels apprehension, disorientation and convulsion result. A severe overdose can lead to medullary depres-

sion resulting in cardiovascular depression and respiratory arrest.

Contraindications to the use of Lidocaine include Stokes-Adams syndrome with A-V dissociation and slow nodal or idioventricular pacemaker.

PROCAINE AMIDE (PRONESTYL)

Pronestyl hydrochloride is p - amino-N (2 diethylaminoethyl) benzamide hydrochloride. It was first used in the treatment of cardiac arrhythmias in 1948. Since that time it has increased in popularity, and today is used frequently as a prophylactic agent after myocardial infarction.

Just where and how procaine amide works on the myocardium is unknown. Its effects are well documented. Procaine amide prolongs the refractory period, slows conduction, depresses excitability and rhythmicity, and is a vagal antagonist.

Oral administration is to be preferred. When parenteral therapy is necessary intramuscular injection is the method of choice. Intravenous use should be limited to extreme emergencies.

Oral dosage is 1 gm stat for ventricular tachycardia followed by .5 - 1.0 gm every four to six hours. For auricular arrhythmias give 1.25 gm stat; .75 gm in 1 hour; .5 - 1 gm every two hours.

Intramuscular dosage is 0.5 - 1 gm every six hours and intravenous dosage is 0.2 - 1 gram.

Procaine amide is useful in the treatment of: atrial flutter and fibrillation of six months or less duration, atrial fibrillation or flutter after myocardial infarction, as a last resort in supraventricular tachycardias; it has a minor role in ventricular premature contractions and a major role in the treatment of ventricular tachycardia.

The only absolute contraindication is hypersensitivity to the drug. The major problem with procaine amide is the fact that it produces severe hypotension after intravenous administration. Large oral doses may produce anorexia, nausea and vomiting as well as urticaria and/or pruritis. There have been reports of a lupus erythematosus-like syndrome in persons on maintenance therapy of procaine amide. Other side effects include agranulocytosis, chills, generalized lymphadenopathy, arthralgias, muscle pain, and eosinophilia.

QUINIDINE

Quinidine is one of the drugs which has been employed for the longest time in treatment of cardiac arrhythmias. It exerts its beneficial effect on arrhythmias by depressing

myocardial excitability, by slowing conduction velocity (on ECG there is a widened QRS complex), and prolonging the refractory period (ECG shows prolonged Q-T interval).

Quinidine is administered primarily by mouth and only in life endangering arrhythmias is intravenous administration used. The dosage for atrial premature contractions is 200 - 400 mg every 4 - 6 hours. For treatment of atrial fibrillation it is best to first digitalize the patient then administer quinidine according to the following schedule: 0.2 gm five times/day at two hour intervals. Increase each dose by 0.1 gm/day until toxicity or reversion occurs. Do not exceed 4 gm daily dose.

Quinidine is most useful for atrial arrhythmias—atrial fibrillation, tachycardia, and premature contractions.

Contraindications to Quinidine include patients with quinine sensitivity and those with partial or complete A-V block. Toxic manifestations of Quinidine include G-I symptoms of nausea, vomiting, and diarrhoea. Rare respiratory paralysis and sudden death do occur. Hypotension commonly follows parenteral administration. Quinidine can also cause myocardial toxicity as manifested by ventricular premature contractions, A-V block, 50% or greater increase in QRS duration, ventricular fibrillation, and ventricular tachycardia.

The treatment of cardiac arrhythmias has moved a long way since the early days. Each day new drugs are being discovered which alter cardiac action. Some of these drugs will no doubt aid in the treatment of arrhythmias, others will not. The drugs which have been presented here are now mainstays in the therapy of cardiac arrhythmias. In five years these drugs may be obsolete and new ones will replace them. In order to keep up with the advancements in this field we must read current journals as they are published.

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Surgical Correction Of Congenital Heart Defects

E. R. Traill 7T1

This article is intended to outline some of the principles relevant to the surgical procedures presently used in correcting congenital heart defects. No attempt is made to describe detailed techniques, which are given in the larger references^{1 2}, or to say that a given technique must be used for a certain defect — which procedure to use, has ultimately to be the surgeon's choice, based on experience and the situation as he finds it at operation.

The paper outlines 5 areas:

- basic physiology
- extracorporeal circulation
- pulmonary hypertension
- palliative procedures
- procedures for total correction

PHYSIOLOGY

The foetal lungs serve no respiratory function, are collapsed, and present a high resistance to blood flowing through them; blood bypasses the lungs via the foramen ovale and ductus arteriosus. The resistance to pulmonary blood flow drops at birth when the infant starts to breathe; closure of the foramen ovale and ductus establishes the route for normal blood flow to the lungs. Failure of the ductus to close is a common congenital defect, and is often beneficial in association with other defects.

Physiologically, two points are worth emphasizing:

(a) SHUNTS

A shunt is an abnormal communication between two points in the circulation, and carries blood from one point to another via that abnormal route. Shunts are of three types: (1) left to right: conducting blood from the systemic side of the circulation to the pulmonary side; (2) right-to-left; (3) balanced: conveying blood equally well in both directions, or not at all.

Shunts are basic to the understanding of many congenital heart lesions. A typical ventricular septal defect (VSD) is a prime example: early in life, this hole in the septum transmits blood from left ventricle (high pressure) to right ventricle (low pressure) — the shunt is left-to-right. In response to the increased pulmonary blood flow, the resistance to blood flow through the lungs may increase to a point where both ventricles have the same pressure, and the shunt becomes balanced. In a severely advanced VSD the shunt becomes right to left; at this time the pulmonary vascular resistance is high and blood flowing from the venous ventricle through the defect to the systemic chamber may give rise to cyanosis. A patent ductus arteriosus (PDA) is normally a good

left-to-right shunt, carrying oxygenated blood from aorta to pulmonary artery.

(b) GROWTH

The question of growth is important in the repair of cardiac defects in infants and children. The use of prostheses, notably valves for replacement, may be limited before adolescence, and suture techniques as in coarctation of the aorta must be considered. Recent work³ shows normal growth of the heart in animals following replacement of a large part of the right atrium with pericardium or synthetic material; this is most encouraging since these materials are frequently required in closure of septal defects, in total correction for transposition of the great vessels (Mustard operation), and in enlarging the right ventricular outflow tract in tetralogies.

EXTRACORPOREAL CIRCULATION

The purpose of cardio-pulmonary bypass is to take over the functions of heart and lungs, when the heart or great vessels are incised. Blood enters the pump from cannulae which are normally placed in the superior and inferior vena cavae (SVC, IVC). The blood is oxygenated in an artificial lung and pumped back to the body through an arterial cannula. This cannula is placed into the aorta in infants; it can be inserted up a femoral artery if that vessel is large enough⁴.

Note that flow using a femoral cannula is retrograde up the aorta to the aortic valve. Work on that valve, using an aortic incision, affects coronary flow since the aorta must be clamped above the incision to create a dry field, and the coronary arteries therefore get no blood for the period of aortic occlusion.

The venous cannulae are ideally large enough to give a good return to the pump, but small enough to allow partial bypass if it is required. In total bypass, the cavae are occluded around the cannulae with a tournique. For partial bypass the tourniques are released, and this allows some blood to run around the cannulae into the right atrium while the rest goes through the cannulae to the pump; the heart then has a minimal load, and the patient is placed on partial bypass before being taken of the pump, at which time the heart takes over the circulation.

During bypass, blood will return to the right atrium and ventricle via the coronary sinus; this appreciable return is picked up by a sucker inserted into the right ventricle. In some cases a vent is placed in the left ventricle as well; this assures that L.V. pressure remains lower than that in the aorta so the aortic valve is held closed and no air can escape into the aorta. A low L.V. pressure also

allows decompression of the lungs which might otherwise become engorged from bronchial blood flow.

It is important that aortico-pulmonary shunts, whether natural (patent ductus) or surgically created (Blalock, Pott's), be closed prior to bypass for total correction. If the shunt is left open, the lungs are subjected to the pressure of the pump, and may get flooded. In addition, it may be difficult to maintain a good systemic pressure during bypass since the aorta decompresses through the shunt. This is probably most relevant to tetralogies who have a palliative shunt created, then come up for total correction.

Hypothermia is frequently used in conjunction with extracorporeal circulation, and may eliminate the need for it. Hypothermia with the cavae occluded allows ample time for repair of simple artial septal defects (ASD), and uncomplicated pulmonary valvular stenosis.

Bypass involves a massive transfusion. As such many donors are required and each is screened for routine antibodies and crossmatched with the patient. Normally one-day-old blood is used, and fresh blood collected for the immediate post-op period. Just prior to bypass, pH of donor blood is corrected, and blood collected in citrate is converted to heparin by adding heparin and calcium to the bag. This allows rapid neutralization of the anti-coagulant after perfusion, and prevents citrate toxicity.

Pumping definitely affects the blood but not usually significantly. Plasma-free hemoglobin of 50 - 60 mg. % is readily cleared, and platelets which are frequently around 80,000 following perfusion normalize by 4 - 5 days post-op. Fibrinogen is given to a few cases, and some require serum albumin if edematous post-operatively.⁵

PULMONARY HYPERTENSION

Active pulmonary hypertension results from a large left-to-right shunt with excessive pulmonary blood flow, the most common forms amenable to surgical correction being the large PDA, ASD, or VSD. The lungs may be subjected to near systemic pressure, and in the infant with a large shunt the over-worked ventricle may fail.

Mitral stenosis or insufficiency can lead to "passive" pulmonary hypertension through pulmonary venous blockage at the left atrium.

The concern over prolonged pulmonary hypertension is that irreversible changes may occur in the pulmonary vasculature — in the final stages the pulmonary arterioles have small lumens giving rise to high pulmonary vascular resistance, and the shunt may become right-to-left.

Patients with high pulmonary vascular resistance are generally poorer operative risks. The potential development of pulmonary hypertension, or the actual presence of uncontrollable heart failure are frequently the reason for early palliation or total correction of a defect.

PALLIATIVE PROCEDURES

These are intended to carry the patient until he is old enough for total repair, or can be done when no definitive correction exists. In cases of inadequate pulmonary blood flow an artificial patent ductus is frequently created by one of the following anastomoses: subclavian-pulmonary artery (Blalock), descending aorta to left pulmonary artery (Pott's), or ascending aorta to right pulmonary artery (Waterston). These all give rise to a left-to-right shunt, and increase pulmonary blood flow.

Anastomosis is SVC to right pulmonary artery (Glenn) is an effective low pressure shunt designed to increase pulmonary blood flow.

Mixing of right and left atrial blood is increased by creating or enlarging an ASD (Blalock-Hanlon), or by shifting, the atrial septum so the right pulmonary veins enter the right atrium (Edward's). These atrial shunts are frequently done in transpositions, and have the added advantage of being readily adaptable to total correction at a later date using the Mustard procedure.

Creating pulmonary stenosis by banding the pulmonary artery reduces pulmonary blood flow and is done to ease congestive failure or reduce pulmonary blood flow frequently associated with a VSD.

BLALOCK SHUNT

This classic procedure was first done by Blalock around 1945, and involves end-to-side anastomosis of a subclavian to a pulmonary artery. To prevent the subclavian from kinking when it is carried down, the one used is opposite to the side to which the aorta arches — this shunt is frequently done in tetralogies, 25% of which have a right aortic arch.

A Blalock is preferable to a Pott's or Waterston in that the size of the subclavian lumen is correct — large enough to give a good shunt, but not so large as to produce heart failure after the shunt. It is also easier to close prior to bypass for total correction. It requires a sufficiently large subclavian to be limited to cases over about 6 months.

The shunt gives excellent results in young tetralogies, as evidenced by increased systemic arterial oxygen and exercise tolerance, and decreased cyanosis and hematocrit.

POTT'S SHUNT

This is an anastomosis of descending aorta to the left pulmonary artery. It has the disadvantages that too large a shunt leads to heart failure, and it is difficult to close prior to total correction at a later date. It is suitable for infants too small for a Blalock, and leaves the right side of the chest clear for a Glenn if required.

WATERSTON'S SHUNT

The ascending aorta is anastomosed side-to-side to the right pulmonary artery. As in a Pott's, the surgeon deter-

SURGICAL CORRECTION OF CONGENITAL HEART DEFECTS

mines the size of the shunt. It is usually reserved for infants too small for a Blalock, and by increasing flow to the right lung, enlarges that pulmonary artery and makes it more suitable for a Glenn at a later date.

Waterstons have been done in a few tetralogies where the initial Blalock has proven inadequate.

GLENN'S SHUNT

The right pulmonary artery is ligated and divided near its origin, thereby directing the SVC flow into the right lung after end-to-side anastomosis of right pulmonary artery to the SVC. This is a low pressure shunt, the success of which depends on two factors: the vessels must be large enough that the shunt does not thrombose — in this respect the shunt is not done before 6 months of age, and may benefit from a previous aortico-pulmonary anastomosis; and secondly, the vascular resistance of the right lung must be low enough to allow flow from SVC to lung under the influence of gravity, venous pressure and negative intra-thoracic pressure. With this in mind, the patient is kept in an upright position in the immediate post-op period, and no blood is taken from the upper extremities to avoid air embolism.

This is a good procedure for tricuspid atresia, and for some transpositions of the great vessels without pulmonary hypertension and the accompanying elevated pulmonary vascular resistance.^{6 7}

(BLALOCK - HANLON, EDWARD'S): CREATION OF AN ASD, AND SHIFTING OF THE ATRIAL SEPTUM

These are intended to create mixing of blood at the atrial level, and are frequently done in infants requiring palliation for transposition of the great vessels. Both are readily adapted to total correction by the Mustard procedure at a later date, since the initial step here is to totally excise the atrial septum. Creation of an ASD can be done using Rashkind's method of balloon septostomy. If this is inadequate the Blalock-Hanlon procedure can be done either from outside the heart, or under direct vision using a right atrial incision with inflow occlusion.

PULMONARY ARTERY BANDING

The object is to create pulmonary stenosis to offset excessive pulmonary flow frequently associated with a large VSD.⁸

TOTAL CORRECTION

PATENT DUCTUS ARTERIOSUS

Correctable at any age, and usually in infancy if the left-to-right shunt is large and causing heart failure. Respiratory infections or respiratory distress may result from the excessive pulmonary blood flow. A continuous murmur is often heard over the mid-left clavicle. For correction, the ductus is ligated, or divided if very large.

COARCTATION OF THE AORTA

This is a constriction of the aorta, usually in the region of the ductus. Because of the constriction, the femoral pulses are weak or absent, and blood pressure is frequently lower in the legs than arms; there may be hypertension in the upper extremities. The intercostal arteries may enlarge giving a shunt across the coarctation, and this may produce rib-notching visible on the x-ray. The defect may be associated with a patent ductus, and be pre- or post-ductal. In this case, both defects are corrected together.

For correction the coarctation is resected and the aortic segments anastomosed end-to-end. To ensure growth of the anastomosis, continuous suture is usually used for part of the posterior row and interrupted for the anterior row.

ATRIAL SEPTAL DEFECT

The defect is closed through a right atrial incision using hypothermia with inflow occlusion for uncomplicated secundum types, and pump support if anomalous pulmonary veins are present. Small defects can be closed rapidly with a running suture. For large holes, a patch is used, and if anomalous pulmonary veins are present the patch is placed so these veins drain through the defect into the left atrium.

Primum type ASD's usually involve one or both atrio-ventricular valves (mitral and/or tricuspid insufficiency).

VENTRICULAR SEPTAL DEFECT

Closure is through a right ventriculotomy or through the tricuspid valve (small defects) with a right atrial incision. It is important to avoid the conducting system and in this regard sutures are limited to the right side of the septum.

The trend, if surgery is required in early life, is to total repair using deep hypothermia. This avoids palliative banding followed by closure at a later time. If the pulmonary artery has been banded previously, the band is removed during total repair and a plastic reconstruction is done on the pulmonary artery.

PULMONARY STENOSIS

Uncomplicated cases are considered operable if the right ventricular pressure exceeds about 75 mm. Hg. For valvular stenosis, a valvotomy is carried out through a pulmonary arteriotomy, using hypothermia with inflow occlusion.

AORTIC STENOSIS

Uncomplicated cases are operable if the systolic gradient across the valve exceeds about 50 mm. Hg. For valvular stenosis, a valvotomy is carried out through an aortotomy.

Replacement of the valve may be needed in later life.

MITRAL INSUFFICIENCY

Isolated M.I. is a rare congenital defect. The regurgitation may lead to an enlarged left atrium, elevated pulmonary wedge pressure, and passive pulmonary congestion.

A plastic repair on the valve may be followed by replacement at a later date. M.I. frequently accompanies primum type ASD's.

TRANSPOSITION OF THE GREAT VESSELS

The aorta arises from the right ventricle and the pulmonary artery from the left. The heart is typically egg-shaped on the x-ray.

Palliation is often required in infancy, using a Rashkind, Blalock-Hanlon, or Edward's technique. For total repair using the Mustard operation, the atrial septum is excised and a pericardial patch sewn in to direct the caval flow to the mitral valve and the pulmonary venous return to the tricuspid valve. Pulmonary hypertension is a contraindication to this procedure. A remarkable rise in systemic arterial oxygen, with decreased cyanosis and hematocrit, follows a successful repair. This procedure has been used in a few adults with good results.^{9 12 13}

TETRALOGY OF FALLOT

The initial operation frequently involves the creation of a systemic-to-pulmonary shunt. These shunts are closed prior to bypass for total repair¹⁴. Total correction is carried out through a right ventriculotomy; any infundibular stenosis is resected, and the VSD closed with a patch that is carried up so the aorta leaves the left ventricle. Pulmonary valvotomy is done if need be, and the pulmonary artery enlarged with a patch if under-developed.

The pre-op heart is typically boot-shaped on the x-ray.

TOTAL ANOMOLOUS PULMONARY VENOUS DRAINAGE

The pulmonary veins drain to a common venous pool that enters the right atrium via the SVC (Darling's supra-cardiac type), directly or through the coronary sinus (cardiac type), or via the inferior vena cava often below the diaphragm (infra-cardiac type). Complex anomalies may be a combination of these. An ASD is necessary for survival. The left heart may be under-developed, and pulmonary congestion may be apparent on the x-ray. These factors must be considered for correction, which includes:

- (a) Anastomosis of the venous pool to the left atrium.
- (b) Closure of the ASD, preferably in such a way as to enlarge the left atrium.

(c) Enlargement of the left atrium by a patch if the left atrial pressure is excessively high after the anastomosis and closure of the ASD.

(d) Consideration of the pulmonary-systemic venous connection. This is frequently a vertical vein (left SVC with no connection to the coronary sinus) draining to the left innominate vein in the supra-cardiac type. Some ligate this vein at the time of total repair; others prefer to leave it open as a means of pulmonary decompression; and ligate it at a later date when the left heart has developed a normal capacity.^{15 16 17}

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Eponyms And The Men

A veritable multitude of cardiologists have achieved eponymous recognition. To follow are but a few:

ADOLF FICK (1829-1901); mathematician, physicist, physiologist. A scientist who made contributions in many fields, he was a quiet, earnest, scholarly man, deeply read in philosophy and literature, and one who did not publish his findings widely, nor exploit them. First educated in mathematical physics at Marburg, he changed to medicine upon the advice of an older brother. Zurich welcomed him for sixteen years and Wurzburg later enjoyed his chairmanship of physiology for the rest of his active life. Early publications included his law of fluid diffusion at the age of 26, and "Medical Physics", a large tome, one year later. The physiology of cardiac muscle contraction, his major interest, led to the famous *Fick principle* of cardiac output, published in 1870. It was characteristic of Fick that this elegant publication satisfied him to the point that he demonstrated no concern for the appearance of its experimental confirmation.

ERNEST HENRY STARLING (1866 - 1927) was hailed as one of the foremost physiologists of his era and is recognized even today as one of the greatest contributors to cardiology and haemodynamics. Born in London, he advanced quickly, entering Guy's Hospital at 16 and being elected a Fellow of the Royal Society at 33. A patron of the basic sciences, his subjects of investigation were those physiological processes which seemed capable of interpretation in terms of physics and chemistry. His laws of cardiac output marked the greatest milestone in the field since William Harvey. They did not, however, obscure his other achievements: (1) elaboration of the conditions determining vascular transudation (2) contributions to gastroenterology through his research on the neuromuscular mechanisms of intestinal movement (3) discovery of secretin (4) maintenance of a functioning mammalian kidney in vitro and subsequent description of renal secretory mechanisms, and (5) toxicological advances in defensive methods against the poisons of gas warfare during World War I. A dedicated humanitarian as well, Starling served as Chairman of the Royal Society's Food Commission and directed efforts to alleviate wartime food shortages.

AUSTIN FLINT SR. (1812 - 1886), whose enonym is the cardiac murmur sometimes heard in aortic insufficiency, was a noted American physician and authority on clinical medicine, percussion, auscultation, phthisis, and medical ethics. A founder of the medical faculty at the University of Buffalo, he lectured there, at Louisville, and at New York's Bellevue Hospital. His later nineteenth-century texts on general and thoracic medicine were highly regarded.

WILLIAM STOKES (1804 - 1878) and ROBERT ADAMS (1791 - 1875), Dubliners, together elaborated the *Stokes-Adams syndrome* of heart block in 1846. Adams was noted for his contributions to the pathophysiology of heart block in 1826 and of rheumatic gout in

1857. Stokes, a colleague of the famed Robert James Graves, acknowledge himself a disciple of Laennec by 1825 with his "Introduction to the Use of the Stethoscope." During the Dublin typhus epidemic of 1826 he laboured for the poor and thereby contacted the fever himself a year later. He survived to report the first case of cholera during the Dublin epidemic of 1832 and to write memorable treatises on diseases of the chest (1837) and on those of the heart and outflow tracts (1854). Honours frequently befell him, first succeeding his father as Regius Professor of Medicine in 1845 and later as one of the few physicians ever to receive the Prussian Order of Merit.

Electrocardiography owes a primary debt to WILLEM EINTHOVEN (1860 - 1927), professor of physiology at the University of Leiden. His string galvanometer offered a distinct improvement upon the capillary electrometer of Augustus Waller, his teacher and predecessor. Einthoven, whose ECG triangle and postulates are fundamental to the science, cooperated with the University Hospital in Leiden by laying a cable between the Institute of Physiology and the clinic. In this way, he "telecardiographed" patients whose ECG patterns could be studied 1.5 kilometres away in the laboratory. In 1924, the Nobel Prize in Physiology and Medicine was conferred upon Einthoven, to whom "honours were a smaller recompense than was the knowledge of the benefits which his long and arduous work had brought to his fellow men", (Sir Thomas Lewis). On the mechanism of cardiac contractility, Einthoven wrote C. J. Wiggers in 1926, "The truth is all that matters; what you or I may think is inconsequential."

JOHN BRUCE MACCALLUM not only made spectacular contributions while a medical undergraduate at this university and at Johns Hopkins, but also witnessed his meteoric career extinguished by tuberculosis at 30 years of age. Taught and greatly admired by Osler, he published and illustrated 27 original papers, six as a student before the turn of the twentieth century. At Baltimore, he produced a classic in the study of the disposition of myocardial fibres; the *MacCallum's patch* of rheumatic endocarditis bears his name. Later, he became a revered teacher in the United States. While music and the theatre provided welcome relief from his ill health, he sketched and wrote poetry to his death. Among his unpublished lines are:

"Oh come, be swift and take me while I stand,
My work still strong beneath a steady hand."

G. D. Hardacre 7T0

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Student Research

A Possible New Approach To The Study Of Metabolism

It is well established that the catecholamines, adrenaline and nor-adrenaline, influence fat and carbohydrate metabolism, and energy production in the mammalian body. Nor-adrenaline and adrenaline are both found in the adrenal medulla in the ratio of 3:1; however, nor-adrenaline alone is found in the sympathetic nervous system where it acts as the nervous transmitter substance. Thus it can be seen that stimulation of the adrenal medulla causes the release of hormones that have similar effects throughout the body as direct sympathetic stimulation. From this it can be seen that there may be a definite relationship between the sympathetic nervous system and metabolism. The field has been reviewed recently by Himms-Hagen¹, however further reference should be made to Feldberg² and Rosenberg³.

The posterior hypothalamus is thought to initiate sympathetic activity. If one could devise a way of influencing this area by the application of various substances—then one might glean some information about the nature of the nervous control of metabolism. Since the CSF bathes this area in the third ventricle—if one could introduce substances in a satisfactory concentration into the CSF, then at least the outer surface of the posterior hypothalamus would be exposed to these substances.

The experimental animal chosen was the dog. Unlike humans, dogs have a very large massa intermedia, and a direct entry into the small 3rd ventricle would be very difficult. Therefore, an approach via one of the lateral ventricles was decided upon. This approach has several advantages; firstly, the lateral ventricle is readily accessible; and secondly, it is the primary source of CSF—thus substances entering here would readily intermix with the CSF via this route.

It is preferable to study animals under as close to normal physiological conditions as possible—ie. conscious, non-anaesthetized, and standing quietly in a Pavlov stand. This means that the dog must not be in pain. Feldberg⁴ has described a painless preparation of ventriculocisternal perfusion in both conscious and unconscious cats; Papenheimer⁵ has described the same for goats.

We, however, were interested in a preparation that would permit re-use of the animal over a relatively long period of time—up to many months if necessary. After several attempts, such a preparation was developed utilizing a thoroughly modified Collison (Feldberg) cannula. Our final approach allowed us to infuse or inject into the lateral ventricle, to remove small amounts of CSF, and to possibly measure the pressure of the CSF. All these procedures could be carried out with ease—and with no discomfort felt by the animal. Now that we had such a

workable and versatile preparation, the road was open to the investigation of our problem. Previous preparations by other investigators uniformly used the ventriculo-cisternal perfusion technique. This method has the advantage of allowing one to perfuse a specific area in the ventricular system with drug or substance, but has the great disadvantage of introducing two holes into the animal's head, and thereby shortening the life of the preparation and upsetting even further the normal physiological state.

Initially we chose the concentrations of glucose and FFA in plasma as the two parameters to be followed. Not only can the actual blood concentrations of these substances be measured, but also their turnover by tracer techniques.

Our experimental work has been seriously hampered by the uncertainty about such basic parameters as the rate of flow and the volume of CSF in the dog (Davson)⁶. Some of the preliminary experiments have shown some interesting results. In the beginning we infused at a very low rate 40 λ /min.—so low in fact that we felt that we could infuse our substances in 0.9% saline. However, it soon became evident that we were causing a definite effect, for after 30 min. the dog became restless, gave a profuse watery salivation and eventually became stuporous. Without fail the dog died after some hours. The blood sugar level rose while the FFA level fell. Subsequent experiments using artificial CSF have proven that these observations were not due to either a decreased glucose level in the CSF or, to an elevated ventricular pressure (caused by too large a volume of fluid being introduced therein). Since Papenheimer⁵ found that by merely reducing the Ca^{++} level to 60% of its normal value the animal reacts in this way—it seems likely that the reaction was due to a lowered $[Ca^{++}]$ in the CSF. Since we are indeed infusing into the system—not perfusing it—the problem of hydrolic pressure building up within the ventricle is a real one. Using artificial CSF and rates of infusion varying from 9 λ /min to 80 λ /min, we found no overt effects in the dog either metabolically or neurologically. The one drug series that has been carried out has been Nor-adrenaline. A concentration sufficient to increase the plasma FFA level two fold, (Nor-adrenaline has no effect on plasma glucose) was chosen (0.1 γ /kilo. min.). When this amount was infused intraventricularly, there was no effect on the peripheral FFA level or the plasma glucose. From this observation one might infer several things; firstly, that the nor-adrenaline did not enter the peripheral blood; secondly that it did not affect any cells (if they are present) that have any direct control over glucose or FFA plasma levels; thirdly, that the nor-

adrenaline was taken up quickly by the cells and stored (in storage granules) without causing any affect, and fourthly, that it was instantly destroyed. This last inference is unlikely since nor-adrenaline is known to be present normally in CSF in a concentration of 2.4 - 3.1 ug/l.⁷. As a follow up to every experimental series, the dogs head is preserved, dissected and photographed to determine the exact site of the cannula.

As stated at the beginning of this report, this method is only now being developed fully and very few results are available. However, it is quite clear that now that the method is workable many results will be forthcoming.

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Assaeries

Heart Substitutes - Special Review

INTRODUCTION

At present the variety of organ substitutes is indeed staggering. In fact it has reached the point where no one practitioner can truly understand and master the array of substitutes for even one organ. It is the intention of this special issue to summarize for those working in the wide field of Applied Cardiology the history and techniques of heart substitution presently practised in medicine. It is our hope that such a review will put this rapidly expanding field back into perspective for those who have specialized and lost track of the more sophisticated advances since graduating from Heart School.

In general, while there are over five hundred specific patented heart substitutes and mechanical aids, there are only four broad categories of true Heart Substitutes. The first of these, the Transplanted Heart (that is, a real homotransplant from a human donor) is so archaic and inefficient as not to warrant serious mention. However, its continued and outdated use in several areas, notably, Johannesburg and Toronto, have kept the method alive; and even today, in Toronto journals, the number of heart-transplant articles is exceeded only by the number of articles on insulin.

The second general group of Heart Substitutes, and historically the first mechanical Heart Substitute to succeed, may be exemplified by the original Wellman Heart of 1997. This model, which included a crude transistorized energy unit and beronium filter trap mechanism for catching dust and crenated poikilocytes was too large actually to be placed inside the chest cavity. It stood twelve feet high and was attached by corrugated teflon tubing to the major vessels of the heart. It required thirty-six pints of blood to prime it, cost ninety-three thousand dollars per year to maintain, and the patient could move

about only by driving it wherever he went (a steering device and gasoline engine were incorporated into the early models). Needless to say, this type is now defunct, although still used in several developing countries.

The third type of Heart Substitute is the one with which most contemporary Applied Cardiologists were trained: the standard double chamber six to ten centimetre Rayalon tubeless "Hartt" with atomic battery. While effectively guaranteeing a previously normal life span of ninety-five or more years, the parts are not interchangeable between models, and few physicians have been able to learn the intricacies of more than one or two; and further, there still remains the unconquered danger of sudden decompensated valvo-vascular disjunction (or "busting a flap" as the Surgeons call it) which can be fatal.

The fourth type of Heart Substitute is still in development but undoubtedly promises the greatest future by far. It is two point eight centimetres in diameter, made of stainless steel and magnesium, powered by Margum Dust (0.03 grams per one thousand years) and is virtually immortal. There are no adequate control studies yet, but the three original recipients (all done one hundred and eleven years ago) are still alive and active in local athletic clubs and youth groups. As a display of its confidence in the possibilities of this Heart Substitute, the government of Sweden has already legalized the substitution of all human hearts at birth (at the parents' discretion, of course). This bold step promises to open up the benefits of this Heart Substitute to all mankind.*

Although the brevity of this introduction implies that these Heart Substitute devices are each quite simple, such is not the case, and I do not wish, to defeat the argument of requiring a six year residency program without pay

before certification of Heart Substitute Specialists. I exhort you to read the more detailed descriptions of each type, which occupy the remaining pages of this issue.

A. J. Shoichet 6T9

*It is unfortunate that similar legislation in other countries has balked at the insistence of the Church; its repeated statements on the Unnaturalness of Heart Substitution (see re-

cent Papal encyclical), despite mounting evidence as to safety and effectiveness, are the only significant barrier to world-wide acceptance. Many Catholic dignitaries have bravely spoken against the Papal stand, suggesting that it may mean the break-up of the Church, but the Pope has been adamant in his Interpretation, and has once more invoked the principle of Papal Infallibility.

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Symptomatology - Pain, Part II

Headache

Headache is a symptom too often dismissed by the physician with a prescription of aspirin or a stronger analgesic. In many cases, the underlying motivation for such action is a fear of the unknown, a reluctance to tackle a vague symptom such as headache as a diagnostic problem. Indeed, headache, or cephalgia, is poorly understood, yet it is one of the important premonitory signs through which our soma may inform the psyche of early pathology. Although many headaches are "idiopathic", a sufficient number represent life-endangering or debilitating processes such that each patient who presents with headache deserves careful evaluation.

The Ad Hoc Committee of the National Institute of Neurological Diseases and Blindness has formulated a useful classification of head pain, based on the mechanism of its causation:

A. Vascular Headaches of Migraine Type

- (I) Migraine (classical)
- (II) Migraine (atypical)
- (III) Cluster headache
- (IV) Hemiplegic migraine and ophthalmoplegic migraine
- (V) Lower half headache e.g. atypical facial neuralgia; sphenopalatine ganglion neuralgia; vidian neuralgia

B. Muscle Contraction Headache (Tension Headache)

C. Combined Vascular and Muscle Contraction Headache

D. Headache of Nasal Vasomotor Reaction

E. Headache of Delusional, Conversion or Hypochondriacal states

F. Non-migrainous Vascular Headaches

- (i) Infection and Fever
- (ii) Toxic (hypoxia, carbon monoxide, nitrites, nitrates, 'hangover' etc.)
- (iii) Hypertension
- (iv) Cerebrovascular malformation

G. Traction Headache

- (i) Neoplasms
- (ii) Hematomas
- (iii) Abscesses
- (iv) Post-lumbar puncture
- (v) Pseudotumour cerebri

H. Headache of Cranial Inflammation

I. Headache due to Disease of Ocular, Aural and Nasal, Sinusal and Dental Structures.

J. Cranial Neuritides

K. Cranial Neuralgias

- (i) Tic douloureux
- (ii) Glossopharyngeal neuralgia

The classification is, to say the least, not a simple one, but it does suggest the multiplicity of origin of cephalgia. Categories A through E comprise the major clinical disorders which are dominated by headache, while the remainder are usually accompanied by symptoms and findings elsewhere. Space does not permit a detailed discussion here of each headache syndrome. An attempt will be made to discuss the basis for several of the important types of headache only.

A brief review of the pain-sensitive structures within the cranium is essential to the understanding of head pain.

Bone—The bony cranium, like all the bone in the body, is not pain-sensitive. The periosteum is, of course, highly sensitive.

Meninges—Both the dura and the pia-arachnoid are extremely pain-sensitive along the courses of arteries and dural sinuses. Otherwise the pia-arachnoid is not pain-sensitive and the dura is sensitive only in certain areas, predominantly infratentorial.

Vessels—Meningial (dural) arteries are acutely sensitive to painful stimuli, and the pain is felt over the affected artery. The dural sinuses are variably sensitive; the superior sagittal, transverse, straight and occipital sinuses respond to painful stimuli, but the inferior sagittal does not. Major cerebral arteries are, in general, sensitive to pain in their most proximal parts only, for a distance of one to two cm; thereafter, they are insensitive. The internal carotid and middle cerebral arteries refer the pain to behind the eye and low in the temporal region, the anterior cerebral and pontine arteries to behind and above the eye and behind the ear respectively, and the posterior or inferior cerebellar and vertebral arteries to the occipital region. Pain arising from cerebral arteries is unilateral and homolateral.

Parenchyma—The parenchyma of the brain is devoid of pain-sensitive nerve endings.

Ventricles—The lateral and third ventricles are sensitive to rapid distension or emptying, giving rise to a diffuse pain. The fourth ventricle is less sensitive to painful stimuli.

Cranial Nerves—Irritation of cranial nerves results in pain, referred to anywhere in their respective sensory distribution. Upper cervical lesions may refer pain as far up as the vertex.

An example of the application of the above anatomical principles follows. Fifty percent of patients with thrombosis of the internal carotid artery have unilateral headache over and behind the eye and low in the temporal region. Thrombosis of parenchymal intracranial arteries produces no pain, because these segments of the vessels are not pain-sensitive. The headache of internal carotid artery thrombosis may accompany episodes of transient hemiplegia, but usually the pain antedates the onset of other symptoms, often by years. The headache is due to inflammation in and about the wall of the artery, with a contribution from tissue ischemia. Thus, familiarity with pain patterns can lead to early diagnosis of internal carotid disease and aversion of a cerebrovascular accident.

TRACTION HEADACHE

It is a misconception that changes in intracranial pressure, per se, give rise to headache. Experimental elevation of intracranial pressure does not in itself cause pain, nor is the association between intracerebral masses and headaches a constant one. What is necessary for production of headache in these cases, is the displacement of structures which contain pain-sensitive nerve endings, so that these endings are mechanically stimulated by the stretching (traction).

About 25% of patients who undergo lumbar puncture suffer from headache following the procedure. Measurements of intracranial pressure have shown that the initial decrease is rapidly compensated for by dilatation of the veins and swelling of the brain. The dilatation and swelling occur because the intravascular pressure exceeds the extravascular pressure after the removal of cerebrospinal fluid, thus distension and transudation take place. Therefore, the headache is not due to changes in intracranial pressure. However, the cerebral edema puts longitudinal traction on the veins, and this, combined with distention of these vessels, produces sufficient mechanical stimulation of the intramural pain fibres to result in pain.

Post-lumbar puncture is characteristically a dull, deep ache, usually bifrontal, but often suboccipital. It occurs a few hours to several days after the procedure, and lasts for hours, days or weeks. It often disappears on lying down and recurs on assuming the erect position. It is made worse by shaking the head and better by tilting the head. Compression of the jugular veins increases the pain and may be useful diagnostically.

The removal of the approximately 10 ml of fluid taken in a routine lumbar puncture is insufficient to cause headache, but continuing leakage of cerebrospinal fluid through the hole in the meninges reduces the C.S.F. pressure enough to cause pain. This accounts for the delayed onset and variable occurrence of post-lumbar puncture headache. From the foregoing, it can be seen that using a small needle, reducing the number of punctures and keeping the patient immobile during the procedure will decrease the incidence of headache.

Cerebral tumours are also associated with a characteristic type of headache. The pain is again deep, aching and dull, usually intermittent and not too severe. Relief is often obtained with aspirin. Rarely is the patient awakened at night by the pain, and the pain is often at its worst in the early morning. Rapidly-growing neoplasms are most likely to cause headache. However, slow-growing infratentorial lesions may often cause headaches, because they frequently produce internal hydrocephalus, which distorts the brain and puts traction on pain-sensitive structures at its base. Slowly expanding supratentorial tumours are least often associated with headache. The location of the pain unfortunately, correlates poorly with the site of the mass. The only constant finding is that unilateral pain produced by tumour, almost always means an ipsilateral mass.

Brain abscesses, as they expand through accumulation of fluid, cause headache by the same mechanism as neoplasms. Systemic signs of infection aid in the diagnosis.

Subdural hematoma, due to rupture of veins leading to the sagittal or longitudinal sinus, is associated with a headache which comes on almost immediately following the vascular accident. The pain is usually dull, diffuse and steady and may increase in intensity during the first

six to eight weeks. At first, the pain may be unilateral, but later it becomes generalized. Ipsilateral pupillary and tendon reflex changes often occur due to pressure on the third cranial nerve and the cerebral peduncle respectively. The C.S.F. may be xanthochromic and the protein content increased.

In summary, all the types of headaches discussed thus far are due to displacement of brain structures, i.e. traction headache. They are dull, with no pulsating quality, and relatively poorly localized.

VASCULAR HEADACHES

Vascular headaches, be they of the migrainous or non-migrainous type, share a common mechanism. In 1933, Pickering and Hess showed that histamine injection resulted in vaso dilatation, a fall in systolic and diastolic blood pressure and a typical cephalgia. Further work revealed that the cerebral vessels remained dilated for a period of time after systemic blood pressure had been restored and that the amplitude of pulsation of these vessels was thereby much wider than normal. The onset of histamine headache corresponded well with the restoration of blood pressure and the conclusion was drawn that headaches of vascular origin are due to the force of a normal or elevated blood pressure on a dilated cerebral vasculature resulting in stretching of the arterial walls.

The migraine syndrome is the most familiar of the vascular headaches. The well-known clinical picture of migranie will not be described here. Of note is the familial tendency of the syndrome, appearing in members of proud families, who stress achievement and suppress aggressive or demonstrative feelings.

It is believed that sufferers from migraine have an abnormal or excessive paroxysmal release of a substance which causes first constriction, and later, dilatation of cerebral arteries. The nature of the chemical is not yet known, but it is unlikely that it is histamine. Research has been concentrated on bradykinin, 5-hydroxytryptamine (5-HT, serotonin) and neurokinin, but definitive evidence favouring any one of these is as yet lacking.

Ophthalmoplegic migraine and hemiplegic migraine are variants of the classical picture. Ophthalmoplegic migraine consists of a severe, prolonged migraine attack followed in two to four days, by aphthalmoplegia. The headache and paralysis are unilateral and ipsilateral. Both oculomotor and pupillary fibres are involved. Usually normal ocular function returns in one to two weeks, but occasional permanent deficits have been reported. Hemiplegic migraine resembles the ophthalmoplegic variety, hemiplegia replacing ocular manifestations.

Cluster headache, also called Horton's histaminic cephalgia, though differing in many ways from migraine (see Table I), is classified with it on the basis of its well-established vascular origin. Horton's carefully documented work describes a unilateral headache which oc-

(After MacNeal) TABLE I: FEATURES OF MIGRAINE, HYPERTENSIVE & CLUSTER HEADACHES

	MIGRAINE	HYPERTENSION	CLUSTERS
<i>Sex Ratio</i>	F = 10 x M	M = F	M = 10 x F
<i>Age of Onset</i>	15 - 30	30 - 50	25 - 50
<i>Periodicity</i>	Irregular, widely spaced	Irregular frequent	"Clusters"
<i>Family History</i>	+	±	—
<i>Time of Occurence</i>	Frequently on waking, occasionally nocturnal	Usually on waking	Most commonly 2 - 4 a.m.
<i>Mode of Onset</i>	Aura, gradual	No aura, gradual	Sudden
<i>Severity of Pain</i>	+++	+	++++
<i>Duration</i>	4 - 25 hrs.	May be constant	1 - 2 hrs.
<i>Vasomotor Phenomena</i> (eye redness, lacrimation, rhinorrhea)	±	0	++++

curs in a series of attacks of short duration. Each attack is of rapid onset and termination, and lasts less than an hour. The pain is extremely severe, usually described as burning or boring in quality. It involves the ocular region, the temple, the neck, face and even shoulders or teeth. During attacks, tenderness may be elicited over the branches of the external carotid artery, and ipsilateral profuse lacrimation, rhinorrhea, perspiration and flushing frequently accompany the pain.

As its eponym would suggest, Horton postulated that cluster headaches were related to a hypersensitivity to histamine. However, his claims for cure through hypsensitization procedures have not been consistently reproduced. Another substance, whose nature remains a mystery, is likely responsible for cluster headaches.

Any situation which results in cerebral vasodilatation can produce a headache of the vascular type. The pain will be pulsatile and fairly severe, and often well-localized. Thus, hypoxemia, carbon monoxide poisoning and anemia, which cause vasodilatation secondary to cerebral hypoxia, often produce a typical vascular-type headache. Nitrites, nitrates and alcohol have a direct effect on blood vassels, as does hypoglycemia, and frequently produce headaches. Fevcr, bacteremia and septicemia are also thought to cause headache through cerebral vasodilatation.

Headache associated with an elevated blood pressure is seen in three situations:

- (a) Headache associated with a sudden rise in blood pressure; probably resulting from dilated intracranial arteries.

- (b) Headache associated with essential hypertension.
- (c) Headache associated with renal failure azotemia, focal brain edema and increased intracranial pressure; similar to traction headache.

The headache of essential hypertension is a dull, deep aching, usually intermittent, but sometimes continuous. The pain may be generalized, unilateral or occipital. It is often worse in the early morning and may awaken the patient. Arising from bed or taking a cup of coffee may diminish the pain, whereas heavy work, bending over or coughing often increase it.

The severity of the headache is not necessarily related to the degree of elevation of the blood pressure. More important is the tone of the cerebral vessels for a moderate degree of hypertension acting on a relatively hypotonic cerebral vasculature will result in a more intense pain than a higher pressure with good tone in the cerebral vessels. Unlike the migraine syndrome, which affects primarily intracerebral vessels, the headache of essential hypertension probably involves the extracerebral (extracranial and meningeal) arteries.

MUSCLE CONTRACTION (TENSION) HEADACHE

Any type of headache may produce tonic contraction of the cephalic and cervical musculature. The pain that arises from the sustained tension in these muscles then becomes superimposed on the primary process and may result in a confusing picture. Since prolonged anxiety as well as trauma to the vertebral column or surrounding tissues can also cause muscle spasm, deducing the chief problem can be difficult in a patient with a tension type of headache. The temporal, frontal and cervical muscles are most frequently involved in tension headaches. However any muscle may be affected, depending on the circumstances. Sustained contraction of the Masseters may give rise to pain in the jaw. This can occur with dental disease or with neoplastic infiltration of the bones of the skull or cervical vertebrae.

The clinical picture of "cephalic myalgia" is typical. The patient usually complains of a band or vise around his head or of crawling sensations, tender lumps, pain on brushing his hair or severe cramps. The symptoms may be unilateral or bilateral and may involve any part of the head. Bright spots before the eyes, tinnitus, and vertigo may occur, particularly with an occipital location of the pain. The duration of the pain is variable, and may be months or years. On physical examination, palpation of the effected muscles will reveal them to be tense and often tender. Tender nodules may be palpable in the muscles.

Once it has been established that muscle spasm is contributing to the headache, a search for primary factors is required. Sedatives, application of heat and psychological support will help to abolish the muscle tension and

its effects. Then a better evaluation of other influences can be made.

The mechanism of the pain arising from sustained muscular contraction is not known, but it probably does not involve a reduced blood supply or tissue ischemia. Studies have shown that blood flow is actually increased in the tonically-contracted cervical musculature.

HEADACHE DUE TO DISEASE OF OCULAR, AURAL, NASAL, SINUSAL AND DENTAL STRUCTURES

Disease of the teeth is a common cause of head pain, but is usually easily recognized. Lesions in the eye which cause headache include glaucoma, refractive errors, muscle imbalance, trauma, and neoplasms. The ear is an occasional source of headache and because so many cranial nerves (5th, 7th, 9th, 10th) supply the aural structures, lesions in the ear may refer pain to many parts of the head or neck.

Sinus disease has been and still is, a popular diagnosis for vague headaches. Actually, disease of the paranasal sinuses is a relatively rare cause of headache, and should not be implicated without considering other possibilities.

Each of the sinuses, when inflamed, refers pain to a specific region of the head. However, experimental stimulation of the nasal and paranasal structures has shown that the turbinate bones and the ducts and ostia of the sinuses are much more sensitive to pain than are the walls of the sinuses themselves. Since anaesthetization of the turbinates with procaine is successful in the relief of sinus headache, it is unlikely that the source of the pain is within the sinuses. The engorged turbinates appear to be the culprits. Shrinkage of the turbinates with drugs such as phenylephrine is effective in abolishing the pain.

Sinus headaches are more common during the day. Frequently they come on shortly after arising and become worse as the day wears on. Maxillary sinus headache however, often appears in the early afternoon. The pain is deep, dull, constant and of low intensity. Acute sinusitis may produce more severe head pain, but rarely as severe as migraine or meningitis. Aspirin or codeine often provides relief. Procedures which elevate venous pressure (straining, coughing, compression of jugular veins) increase the pain, as does shaking the head.

Williams describes a headache which is episodic, severe and of short duration, associated with chronic bacterial infection of a maxillary sinus. The pain appears most commonly in the early morning and is accompanied by homolateral conjunctival congestion and tearing. However, the headache is probably secondary to a vascular phenomenon unlike other sinus headaches. Williams postulates that neurogenic vasodilation of the supraorbital artery and stimulation of the lacrimal gland produce the syndrome. Pressure over the supraorbital foramen or ipsilateral carotid artery, or washing the purulent ma-

terial out of the affected maxillary sinus relieves the pain. The reason for the association of the vascular changes with sinus infection is unknown.

CRANIAL INFLAMMATION

Inflammation of cranial arteries is a relatively rare, but quite well known, cause of headache. Temporal arteritis is the best documented of the cranial arteritides. Two types of temporal arteritis exist; the term most commonly refers to a benign, often isolated, arterial inflammation, but inflammation of the temporal artery may be part of a widespread disease, periarteritis nodosa. Since the histology of the two types is strikingly similar, they may be closely related.

The benign form of temporal arteritis has systemic, as well as local, manifestations. The local lesion appears to be a giant cell arteritis involving most often a temporal artery, but occasionally effecting the renal, coronary or cerebral vasculature. The usual case presents as headache, with eye involvement due to spread to the ophthalmic artery causing visual deficits in about 50% of cases. Less frequent presentations include unexplained blindness, obscure fever, gangrene of the tongue or otolaryngological disorders (due to involvement of maxillary arteries). Systemic manifestations such as nausea, vomiting, anorexia and weight loss are common. The sedimentation rate is elevated.

The headache of temporal arteritis is intense, well-localized to the affected vessel, and aching in quality, but with a peculiar burning sensation also. The artery is distended, palpable and tender and local redness and swelling may be present. In some cases, biopsy of the artery has been therapeutic. It is interesting that prior to onset of the typical headache, the patient has often had pain in the jaw, neck, teeth or occiput, indicating that the arteries supplying these structures are affected. The disease usually runs a self-limiting course, resolving spontaneously in one to twenty months. The only common residuum is blindness, occurring in a small percentage of cases. Steroid administration speeds resolution and decreases eye involvement.

The aetiology of this disease is conjectural at the moment. A mild leucocytosis is usually present, and the eosinophil count is normal, so an infective rather than an allergic factor is most likely. In about one-half of the cases, there is evidence of a preceding or concomitant infection in the head, often in the teeth or gums, suggesting the direct spread of local infection along blood vessels as a reasonable hypothesis. However, organisms have not

been consistently recovered from the region of the inflamed arteries.

Another inflammatory process producing headache is subarachnoid hemorrhage. A pain of sudden onset and of high intensity must arouse suspicion of this process. Often the pain is occipital in location and may be associated with vomiting drowsiness or coma. Neck rigidity is almost always present. One-third of patients with subarachnoid hemorrhage do not survive the first episode. The remainder have a reduction in intensity of their pain in a few days and complete elimination of headache within two months.

The initial pain of subarachnoid hemorrhage is probably due to traction of intracranial structures. The persistence of pain is related to sterile inflammation of the blood vessels and meninges.

T. F. Shapiro and Z. Cohen

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Clinicopathological Conference

Progressive Dyspnoea

CASE PRESENTATION

This 65 year old white male presented on June 1, 1967 with a four year history of increasing dyspnoea.

Past history revealed that the patient had been in good health until 1960 with no evidence of respiratory dysfunction. At this time he developed bilateral lobar pneumonia for which he was treated at home for one month. He recovered and was apparently well until 1963, at which time an episode of bilateral viral pneumonia was again treated at home. In the next year the patient complained of generalized weakness, fatigue and progressive shortness of breath on exertion. There was no history of respiratory allergies, tuberculosis or previous pulmonary infections. He had smoked a package of cigarettes per day for over 40 years. A history of exposure to noxious fumes, dusts or specific pollution was absent. He was employed as a safety supervisor at T. Eaton Company. The family history was incomplete but revealed one sister with pulmonary emphysema. He was admitted to hospital for the first time on April 29, 1964 for investigation of this problem.

Functional enquiry was negative. The occurrence of double vision, dysphagia or specific motor weakness could not be elicited.

Physical examination revealed a patient who appeared chronically ill with weight loss. Chest expansion, air entry and breath sounds were normal. There was no swelling of the ankles, jugular venous distension nor signs of deficient cardiac output. The remainder of the physical examination was also normal.

The clinical suspicion of myasthenia gravis was not confirmed by the tensilon test. Thyroid indices and a glucose tolerance test were normal. ACTH tests showed a normally reacting pituitary-adrenal axis. Likewise the ECG and an upper GI series revealed no abnormality. The chest x-ray showed a diffuse honeycomb pattern compatible with pulmonary fibrosis most marked in the lower lobes of the lungs. In an attempt to explain the chest x-ray changes, a scalene node biopsy, mediastinoscopy and a lung biopsy were performed. No evidence of disease process was revealed by the initial two procedures.

Other laboratory examination results are outlined below. Urinalysis, Hb, wbc count, serum electrolytes and CO₂ content were normal. The total serum protein was 7.5 gm% with an A/G ratio of 4.6/2.9. The serum protein electrophoresis produced the following fraction re-

sults (normals in brackets): albumin 66.0 (63.4-78.2), alpha₁ 1.9 (2.1-3.3), alpha₂ 8.5 (4.4-7.6), beta 13.1 (5.1-9.1), gamma 10.5 (8.3-18.5). The eosinophils were 4% in the peripheral blood smear with a total eosinophil count of 516/cmm. The LE cell tests were negative. CCF was 1⁺, serum GPT was 18 and the Van den Bergh was 0.4 mg%. Sputum culture grew normal respiratory flora. Sputum cytology revealed no malignant cells but many histiocytes were seen. A Paul-Bunnell test was negative.

Three months after discharge pulmonary function tests were obtained and chest x-rays were repeated. Forced vital capacity was 3250 ml (86% of normal) and after bronchodilator 3350 ml (89% of normal). Forced expiratory volume (FEV₁) was 71% of the VC and 72% after bronchodilator, (normal being greater than 70% of the total VC). Maximum voluntary ventilation was 125 L/min (120% of normal). Observed diffusing capacity was 9.5 ml/min/Hg at rest with a normal greater than 12. Fractional carbon monoxide uptake at rest was 23% (normal greater than 38). Respiratory rate was 21/min. tidal volume 962 ml and minute volume 10.6 L/min/M².

Radiological examination demonstrated the diffuse bilateral pulmonary fibrosis revealed in earlier films with a slight increase in density and distribution during the 3 month interval. Both sets of x-rays showed markedly more involvement than films taken in 1963. There was no evidence of calcification or cavitation in any of the lesions which were more obvious in the lower lobes.

The patient was treated with Prednisone and examined regularly by his personal physician until his next hospital admission in March 1967. At that time he experienced an exacerbation with increasing dyspnoea, slight cough and production of thick yellowish sputum.

On physical examination his B.P. was 115/75, pulse 80 and respirations 24/min. He was dyspnoeic with slight cyanosis of the lips and nail beds. Examination of the chest revealed decreased chest excursion and decreased air entry bilaterally with a few rales in the right base.

Chest x-ray did not rule out the possibility of a superimposed pneumonic infiltration in the left lower lung field. Since 1964 there had been a marked increase in pulmonary fibrosis. The cardiac outline was no longer clearly seen, with blurring of the diaphragm. There was extensive mottling in both middle and lower lung fields but to a lesser degree in the apical regions. No evidence

of pleural effusion, pleural thickening or abnormal cardiac size or configuration was visible. The main pulmonary arteries were prominent.

Further pulmonary function studies showed a decrease in forced vital capacity (74% of normal). FEV₁ was 78% of VC. However maximum voluntary ventilation decreased to 50% of normal and tidal volume to 840 ml. These changes indicate a restrictive defect. The diffusing capacity was not done.

Admission laboratory examination results were a normal urinalysis, Hbg of 13.3 gm% with a WBC count of 7,380. The peripheral blood smear showed some macrocytes, occasional polychromatophilic cells and microcytes. The BUN and electrolytes were normal, CO₂ content was 18.5 mEq/L. and blood sugar was 144 mg%. Nose and throat swabs grew normal bacterial flora but sputum culture showed an abundant growth of *A. Aerogenes*. The ECG was normal.

Treatment included Tetracycline 250 mg q.6.h, Prednisone 20 mg daily and *Benylin expectorant. Acetyl cysteine and Isuprel were added to the regimen after consultation. Prednisone dosage was reduced to 10 mg. daily and Penicillin V 250 mg QID added because of an increase in sputum production.

After discharge the patient remained at home on Prednisone and continued oxygen therapy. However due to his increasingly crippling dyspnoea he was readmitted to hospital on June 1, 1967. One week prior to admission he was unable to move his feet out of bed and on admission had difficulty chewing.

Physical examination revealed a blood pressure of 110/85, pulse 105/min, and respirations 24 per min. On examination of the chest breath sounds were easily heard and vocal fremitus was generally increased. Inspiratory crepitations were present over the entire chest but no rhonchi were noted. There was no SOA and on abdominal palpation a soft non-tender liver margin could be felt 3 cm. below the costal margin.

Urinalysis was negative, Hbg was 12.8 gm%, WBC count was 9,700 with mild anisocytosis and an increased number of polychromatic macrocytes on the peripheral smear. Arterial blood gas results showed a CO₂ content of 24 mEq/L., pCO₂ of 32.5 mm. Hg and O₂ saturation of 85%. The ECG revealed minor evidence of right ventricular strain but there was little deviation from normal limits.

The patient was treated with Prednisone 5 mg q.6.h., Librium and Valium. On June 5, Prednisolone 10 mg IM q.8.h. was substituted for oral Prednisone therapy. The patient died later the same day.

This case was presented to Dr. Cameron C. Gray of Toronto General Hospital for a clinical discussion and differential diagnosis.

DIFFERENTIAL DIAGNOSIS

In discussing this patient's problem, there are certain features from the history, the physical findings, the laboratory results and the chest x-rays that suggest a diagnosis. Basically this man complained of shortness of breath brought on initially by exertion, but in the latter course of his illness this symptom was present at rest. This shortness of breath was not accompanied by cough, sputum, or wheezing noises in the chest. There was the added observation that oxygen was used with some benefit and terminally that oxygen was required even at rest. From history then, it is apparent that this patient's main pulmonary problem was a marked disturbance in diffusion of oxygen from the alveoli to the capillaries. Throughout the period of his illness another complaint was weakness, which progressed to the point of the patient requiring to be fed his meals. Does this weakness result from the probable low oxygen saturation in the blood and tissues, or does it suggest some other disease process such as adrenal insufficiency or myasthenia gravis?

The physical examination revealed a chronically ill man in respiratory difficulty. At a later stage in his illness there was cyanosis of the nail-beds. No comment was made about clubbing of the fingers on his first admission, and the chest was apparently clear on examination. On a later admission there was decreased expansion of the lungs, markedly decreased air entry and a few rales at the right lung base. On his final admission inspiratory rales were heard over the entire chest. The blood pressure was low normal at 110/85. The rales heard during inspiration only suggest an interstitial reaction or pathology in the terminal air ducts. This finding on examination, along with the history of effort dyspnoea, directs attention to the alveolar walls and interstitial tissues as the likely site of the pathological process.

The laboratory results were helpful in both a negative and a positive way. Some diseases suggested by history such as Addison's disease, myasthenia gravis, thyroid dysfunction and diabetes mellitus, were eliminated by special procedures. Sputums were negative for malignant cells. One sputum on culture grew *A. aerogenes* and this might not have been a pathogenic organism in a patient with a chronic pulmonary disease process. The peripheral blood smear showed macrocytes and polychromasia on two separate occasions. Could this be a response to low oxygen tension of the tissues and the bone marrow in particular? The blood gases were only done on his last admission and there was low oxygen saturation at 85% and this was presumably while receiving oxygen.

In 1964 the pulmonary function studies showed normal tests for ventilation but there was a diffusing defect. By 1967 there was a moderate restrictive ventilatory defect, and no obstruction disturbance. Diffusion capacity tests were not carried out.

It seems likely that a diagnosis of sorts was made in 1964 at the time of the lung biopsy. In any event, the scalene node biopsy and the mediastinoscopy were negative.

The radiographic findings in this case were very prominent and very important. From the time of the first hospital admission to the final hospital period the chest films were described as showing an interstitial fibrotic reaction. There were progressive changes over the period of observation with comments made that the heart borders were indistinct and this suggests an overlying and adjoining parenchymal process. At a later stage in the illness, not only were the pulmonary changes very pronounced from top to bottom, but also the descriptive term of honeycombing was used. This picture, honeycombed lungs, is characteristic of an interstitial reaction, though not specific for any one condition. No pneumothorax was ever noted and clean-cut bullae were described. Also at no time was a pneumonic alveolar infiltrate noted.

The treatment of this patient did not help the patient very much, though possibly his clinical course would have been shorter had he not received corticosteroids and oxygen. It might also be stated that the types of therapy used did not help the discussant to arrive at a diagnosis as the treatment was obviously non-specific and basically ineffective. A point in passing might be made about the long term use of moderately high doses of Prednisone (any corticosteroid) without recording an old Tuberculin test. The use of prophylactic I.N.H. is mandatory in the O.T. positive patient, on corticosteroids, and in the patient with a past history of tuberculous infection or an x-ray picture of granulomatous disease of possible tuberculous aetiology.

In attempting to arrive at a diagnosis in this patient, there is evidence from history, pulmonary findings and pulmonary function studies, to indicate that the patient fitted into the group of the so-called alveolar-capillary block syndrome. Also from the radiological picture the pulmonary changes were chiefly, if not solely, interstitial and the group of diseases that make up the honeycomb lungs need consideration. For the sake of brevity, some of the diseases that result in the alveolar-capillary block syndrome will be listed:

- (1) Pulmonary Granulomas, e.g. sarcoid, berylliosis, histiocytosis X.
- (2) Scleroderma.
- (3) Interstitial Pneumonias—Rickettsia, viral, etc.
- (4) Chronic passive congestion.
- (5) Bronchiolo-alveolar cell carcinoma of lung.
- (6) Schistosomiasis (rare in this country).
- (7) Drug Reactions — hexamethonium, hydralazine, etc.

- (8) Unknown causes of so-called Hamman-Rich type.

Then listing some of the causes of the honeycomb lung:

- (1) Pulmonary granulomas of sarcoidosis, berylliosis, histiocytosis X. (eosinophilia granuloma)
- (2) Scleroderma.
- (3) Infections-treated tuberculous pneumonia with survival.
- (4) Malignant disease-lymphocytic carcinoma (rare).
- (5) Fibrocystic disease of pancreas.
- (6) Tuberous sclerosis.
- (7) Bronchiolar Emphysema.
- (8) Unknown causes—diffuse interstitial fibrosis of the Hamman-Rich type.

The duration of the patient's illness, the lack of abnormal findings, apart from the chest disease, the slowly relentless course to death, unaffected significantly by treatment, suggest that the diagnosis is either bronchiolar emphysema or diffuse interstitial fibrosis of lungs of unknown cause.

A final diagnosis is difficult to make in this patient but the pathophysiologic disturbance fits best an interstitial reaction. The major physiologic disturbance was a diffusion defect. The main radiological abnormality was an interstitial reaction with honeycombing. As previously noted, there was no description of any other organ or system involved apart from the lungs. Though this is possible in both sarcoidosis and eosinophilic granulomas it is most uncommon. The patient with sarcoidosis rarely dies from respiratory failure in a 3 or 4 year period from the onset of symptoms. Also the scalene node biopsy or tissue taken at mediastinoscopy would almost certainly have been positive in a patient with extensive pulmonary involvement due to sarcoid. The same might be said for eosinophilic granuloma with respect to duration of symptoms from onset to death. This disease may involve lungs only though usually in the terminal state right heart hypertrophy and failure is present. A lung biopsy may be necessary to establish the diagnosis of eosinophilic granuloma.

Bronchiolar emphysema is a distinct possibility but usually in this disease cough and sputum, in addition to dyspnoea, are prominent symptoms. Also spontaneous pneumothorax is fairly frequent and clubbing of the fingers is common. The pulmonary function studies show a severe restrictive and diffusion defect as a rule.

The probable diagnosis is diffuse interstitial fibrosis of unknown aetiology. This disorder has none of the features of granulomatous, infectious, or malignant disease pathologically. Some authors have introduced the term—diffuse fibrosing alveolitis—to cover the broad spectrum



FIG. 1. Honeycomb pattern.



FIG. 2. Fibrosis, cellular infiltrate, irregular air spaces.

of pulmonary fibrosis of unknown cause beginning at one end with a minor interstitial fibrotic reaction and a major alveolar exudative reaction such as is seen in degenerative interstitial pneumonitis (D.I.P.). At the other end of the scale is the grossly distorted lung architecture secondary to marked interstitial fibrosis with a minimal intra-alveolar exudate.

FINAL DIAGNOSIS

Diffuse Interstitial Fibrosis of Lungs (Diffuse Fibrosing Alveolitis).

PATHOLOGICAL REPORT

On gross examination the right lung weighed 900 gm and the left lung 750 gm. There was diffuse severe fibrosis and emphysema of both lungs resulting in a honeycomb pattern (Fig. 1). The fibrosis was quite marked and each cut made in either lung revealed dilated air spaces from 0.25 to 2 cm in diameter separated by firm lung tissue. The septae stood out prominently.

The heart weighed 400 gm. The left and right ventricle thicknesses were 1.6 and 0.4 cm respectively. The tricuspid valvular orifice circumference was 16.0 cm, indicating right ventricular dilation and some right ventricular hypertrophy.

Microscopic examination of a lung biopsy on a previous hospital admission (Fig. 2) showed a segment of lung extensively replaced by fibrous tissue. Loose collagenous tissue surrounded irregular air spaces, many of which were lined by cuboidal alveolar epithelium and contained proliferated alveolar cells. Bronchiolar epithelium lined other air spaces some of which contained mucous. The fibrous tissue contained a moderate infiltrate of lymphocytes, plasma cells, a few dust-filled macrophages and a rare foreign body granuloma. In the small areas with alveolar structure preservation, the air spaces were filled with oedema fluid and a few giant cells surrounded by irregularly thickened alveolar walls. Hyperplasia of muscle was not striking and only occasional arteries had any medial thickening.

The sections of lung taken at autopsy were similar. It was remarked that the bronchiolar and alveolar epithelium did not show any atypicality. The lung throughout was markedly congested. As with the biopsy the findings were non-specific.

The extensive squamous metaplasia slightly suggests a preceding viral infection but there was no evidence of any nuclear abnormality. The findings are compatible with the late stages of idiopathic diffuse progressive fibrosis. Progressive systemic sclerosis is also worthy of consideration but can be excluded in the absence of signs elsewhere.

DISCUSSION

In 1944 Hamman and Rich described a condition of diffuse interstitial pulmonary fibrosis of unknown cause. Hamman-Rich disease is an acute fibrosing inflammatory process of the alveolar septae throughout the lung. It is now recognized to be less common than a similar entity of more chronic duration.

The cause of the condition remains unknown. A prerequisite for inclusion in this group is the absence of systemic disease. However similar pathologic patterns may result from a variety of collagenous and chronic infectious disorders. As in renal pathology, etiology may become obscure in an "end-stage" lung.

The association of rheumatoid arthritis with interstitial pulmonary fibrosis suggests the possibility of an anarthritic form of rheumatoid disease. However the pertinent serological tests are usually negative. An infectious etiology appears to be involved in the present case. Such an onset is uncommon in this disease and there is no increase in incidence after viral epidemics. Bonnani et al described an unusual family in which idiopathic pulmonary fibrosis appears to be genetically determined. All affected members were dysproteinemic as well.

Eosinophilia and hypergammaglobulinemia reported in some cases have been interpreted to support an allergic etiology. However a familial or personal history of asthma, rhinitis or atopic eczema is rarely obtainable. Experiments on animals have suggested an autoimmune etiology. The presence of hypergammaglobulinemia, lymphocytic and plasma cell infiltration, circulating antibodies and response to steroids are the accepted autoimmune criteria. Generally the final criterion is only partially fulfilled. The effect of a circulating humoral substance promoting alveolar wall oedema is another interesting possibility. Because of the variety of historical and serological profiles, it is possible that specific etiologic factors vary in each case.

The clinical presentation is typical. Progressive dyspnoea is invariably present. A chronic cough productive of scanty amounts of sputum and episodes of recurrent acute pneumonia commonly are involved. Also frequently associated are loss of weight, diffuse chest pain unrelated to exertion or deep breathing, and degrees of clubbing. Post-tussive rales are often heard in more acute cases over the lower half of the chest. Rhonchi are usually absent. Tachypnoea, especially on mild exertion, indicates the physiological attempt to compensate for decreased tissue compliance.

Radiologic examination is invaluable with respect to grading, progression and prognosis. Lung-field mottling progresses from a "ground-glass" low density consolidation to fine mottling with discrete shadows, the appearance of translucencies and development of a honeycomb lung. Shadows are most common in the lower zones.

Fissure displacement and mediastinal shift may result from lobar shrinkage. Evidence of cardiac enlargement and pulmonary artery dilation suggest complicating pulmonary hypertension and secondary right ventricular hypertrophy. Occasionally radiologic examination is normal on clinical presentation.

Scalene node biopsy has proven to be of no value in the diagnosis of pulmonary fibrosis. Mediastinoscopy may reveal evidence of lobar contraction.

The physiologic basis for the clinical respiratory distress relates to the described pathologic changes. Three affective physiologic abnormalities coexist:

- a. a disturbed ventilation—perfusion ratio,
- b. a diffusion defect,
- c. an increased lung tissue resistance.

An abnormal ventilation-perfusion ratio may occur in two different ways. Either reduced perfusion of the respiratory membrane or hypoventilation of the normally perfused alveolus may be the primary factor. In this disease a diffuse emphysemic effect causes selective alveolar hypoventilation and a resultant detrimental pulmonary venous admixture.

The diffusion defect in diffuse pulmonary fibrosis has been described as the "alveolar-capillary block syndrome". This results in a significant alveolar capillary O_2 tension difference. The diffusion coefficient of CO_2 is twenty times greater than that of O_2 . Therefore the hypoxemic stimulus to respiration becomes relatively more important than in the normal person.

An increased lung tissue resistance four times greater than normals of the same age has been demonstrated in fibrotics. There is no significant difference in airway resistance. Lung tissue resistance is much higher during spontaneous breathing than during panting (low tidal volume). Perhaps it is a function of the degree of the elongation of the compliant elements. Presumably shallow tachypnoea would be a more effective manner of breathing with respect to work load involved. There is an inverse relationship between lung tissue resistance and compliance. However there seems to be no relationship between resistance or compliance and the severity of impairment of gaseous exchange. The pathologic alteration producing a measurable alveolar-capillary O_2 gradient may be independent of the fibrosis responsible for lung stiffening.

On exercise a decrease in arterial O_2 tension has been found. The three physiologic abnormalities again contribute. In exercise the ventilation-perfusion ratio does not improve and may decrease with increasing perfusion of hypoventilated areas. The diffusion defect tends to decrease the contact time between the erythrocyte and alveolar gas to under a critical value. The tissue resistance

changes direct the increased ventilation to the more compliant areas which are already hyperventilated at rest.

The prognosis depends on the acuteness of the disease, the age at clinical onset, the response to steroids and the presence of cardiac or respiratory failure. Classical Hamman-Rich disease is of less than six months duration. However a chronic course may be only slowly progressive over a number of years. Such a course is more common in the older age group but exceptions are numerous. Corticosteroids have proven to be the only drug of value in treating the disease. They suppress inflammatory reaction but existing fibrosis is not affected. During therapy the increasing alveolar-arterial O₂ difference may be reversed indicating an effect on the abnormal ventilatory-perfusion conditions. Reversibility of ventilatory impairment during long term steroid administration is best related to the degree of absence of radiological honeycombing rather than to the amount of functional impairment. However in most cases the prognosis is relatively poor. Death usually occurs within two to six years.

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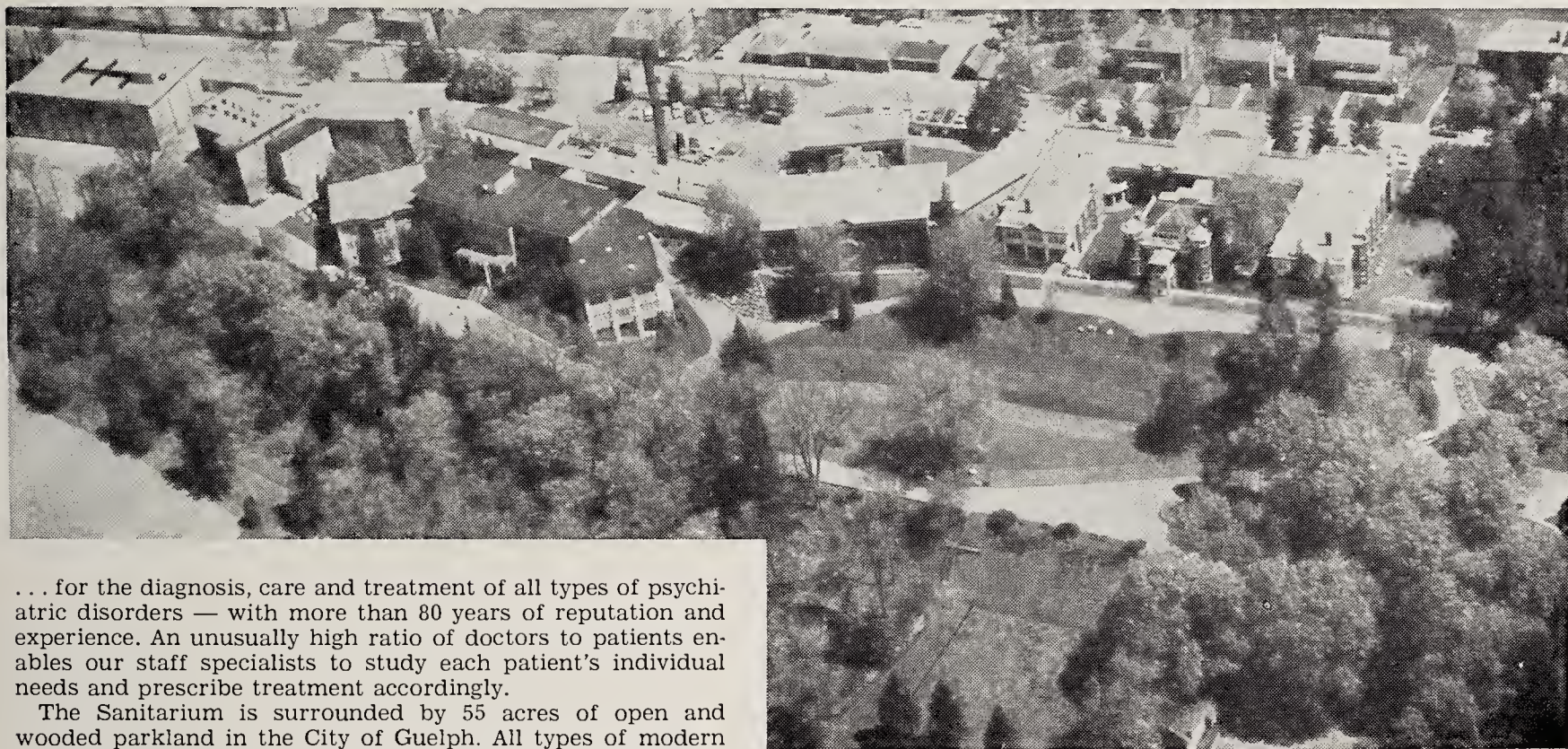
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